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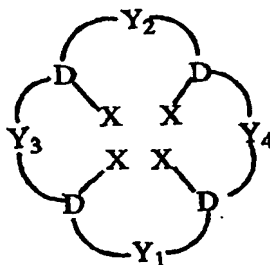
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(54) Title: LONG-LIVED HOMOGENOUS AMIDE CONTAINING MACROCYCLIC COMPOUNDS



(57) Abstract

A robust compound is provided having formula (1) wherein Y₁, Y₂, Y₃ and Y₄ are oxidation resistant groups which are the same or different and which form 5- or 6-membered rings with a metal, M, when bound to D. D is a metal complexing donor atom, O or N. Each X is a position for addition of a substituent and, when D is N, each position is (i) not occupied such that a double bond is formed between D and an atom adjacent to D, or (ii) is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, phenoxy, halogen, halogenated alkyl, halogenated aryl, halogenated alkenyl, halogenated alkynyl, perhaloalkyl, perhaloaryl, a substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted cycloalkenyl ring, a substituted or unsubstituted saturated heterocyclic ring, a substituted or unsubstituted unsaturated heterocyclic ring, and at least one X is hydrogen, and when D is O, the position is not occupied.

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TITLE: LONG-LIVED HOMOGENOUS AMIDE CONTAINING MACROCYCLIC
COMPOUNDS

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH: This work was
5 supported by the National Institutes of Health, GM-44867 and the National Science Foundation
CHE9319505. The U.S. government may have rights in this invention.

BACKGROUND OF THE INVENTION:

This invention relates to metal chelate complexes for forming oxidation catalysts, and
more particularly, to long-lived macrocyclic oxidation activators capable of initiating the
10 catalysis of demanding oxidations with peroxidic and related primary oxidants.

Description of the Invention Background:

While transition metal-based systems provide the major source of oxidants in both
chemistry and biology, oxidation chemistry is much better developed in the latter area, i.e.,
many difficult selective oxidation reactions that are accomplished in biological processes
15 have not been achieved in homogeneous synthetic systems. This difference is more glaring
for oxidation chemistry than for any other major branch of reaction chemistry. Thus,
compared with reduction chemistry or carbon-carbon bond forming chemistry, oxidation
chemistry is still severely limited in the number and quality of the available technologies for
stoichiometric or catalytic processes.

20 The relative dearth of good homogeneous oxidation systems and catalysts is believed
to be due to oxidative degradation. Complexes of high oxidation state middle and later
transition metal ions, analogous to those that function as active intermediates in numerous
enzymatic oxidations, have been difficult to attain synthetically because of the tendency of
such complexes to quickly degrade their ligands.

25 In Collins, T. J., "Designing Ligands for Oxidizing Complexes," *Accounts of
Chemical Research*, 279, Vol. 27, No. 9 (1994), synthetic metal-based oxidants are
conceptually separated into two classes, metalloredox-active oxidants and metallotemplate
oxidants. In metalloredox-active systems, the oxidizing moiety contains the metal ion which
is in direct contact with the ligands. Consequently, these systems are limited by the small
30 supply of ligands that are compatible with oxidizing metal ions. Metallotemplate oxidants

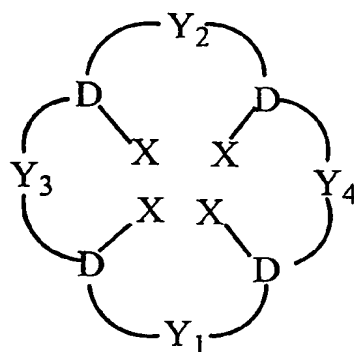
are not limited in such a way because the oxidizing entity is more remote from the metal ion, but metallotemplate systems are useful only for mild as opposed to rigorous oxidations that require highly reactive metalloxidants. The metal ion oxidants in oxygenase enzymes often catalyze rigorous oxidations such as the methane monooxygenase reaction, i.e., the oxidation of methane to methanol with oxygen as the primary oxidant. The roles of the metallo-oxidants in such enzymes are of the metalloredox-active type. Thus, a key to moving this spectacular enzymatic chemistry into man-made systems lies in conquering the challenge of developing robust ligand systems that can tolerate extremely strongly oxidizing metal ions of the atom-abstractor type.

In the *Accounts* article, Collins describes a design-oriented approach to formation of ligands and metal chelate complexes that are resistant to oxidative degradation. The *Accounts* article highlights a set of rules for attaining ligand systems that are inert to oxidative degradation. Several diamido-N-diphenoxido acyclic and tetraamido-N macrocyclic ligands, developed to be resistant to oxidative degradation, are also illustrated in the *Accounts* article, as are middle and later transition metal complexes where the metal ions are in rare or unprecedented high oxidation states attainable by employing the macrocyclic ligands.

While being sufficient to allow preparation of the described rare high valent ions in stable form, including strong electron transfer oxidants, the set of rules of the *Accounts* article is incomplete for achieving the goal of encapsulating an especially powerful metal-oxo oxidant similar to those found in monooxygenase enzymes such that the oxidant has a sufficient lifetime to carry out bi-molecular oxidations. Attainment of such a goal had to wait to the developments in ligand design described herein.

BRIEF SUMMARY OF THE INVENTION

The desired ligand and derivative complex stabilities are met by the macrocyclic tetradentate ligand compound of the present invention. The compounds have the general structure



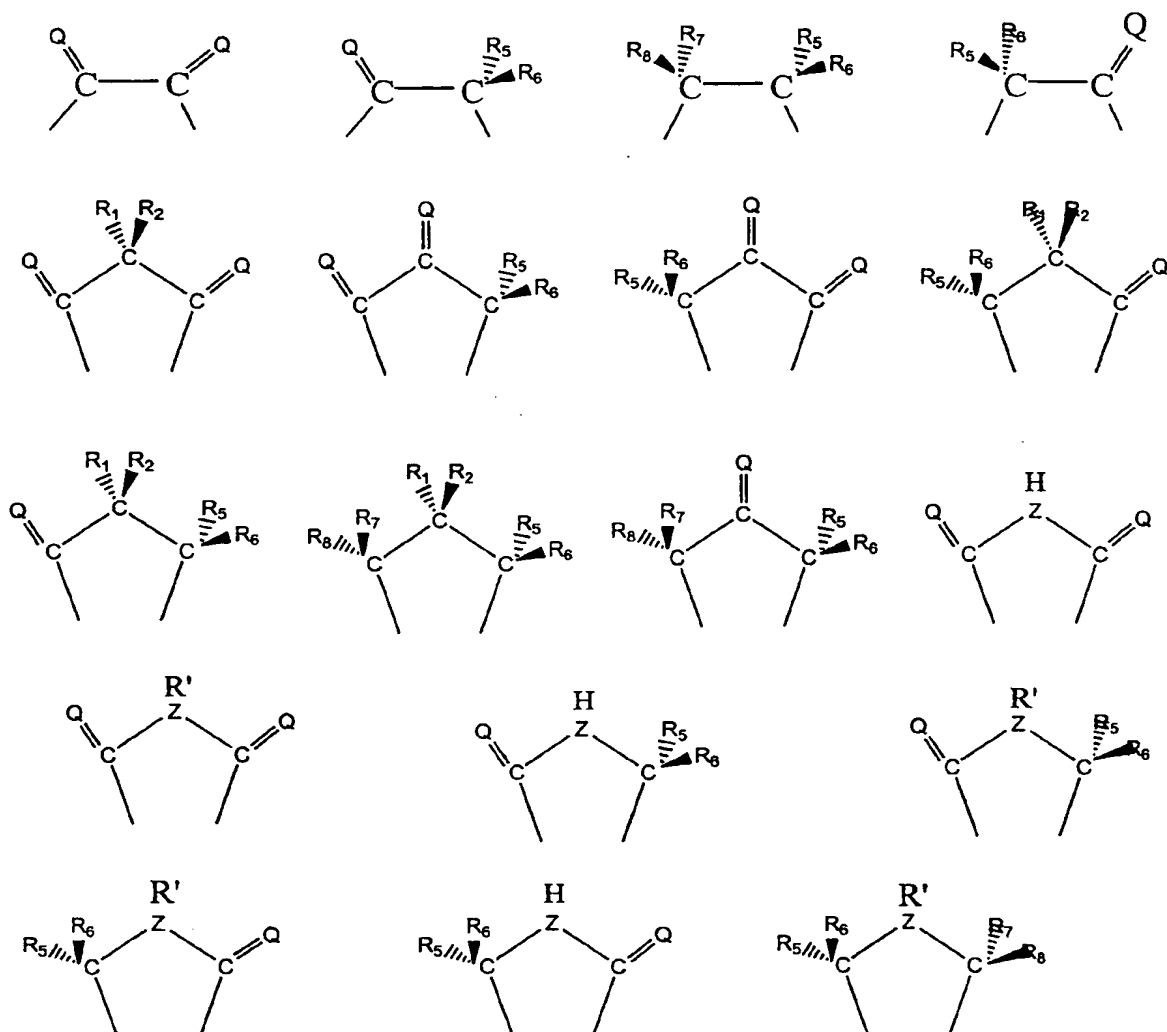
(Compound 1)

wherein:

D is a donor atom selected from the group consisting of N and O;

- each X is a position for addition of a substituent and, when D is N, each position is (i) not occupied such that a double bond is formed between D and an atom adjacent to D, or (ii) is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, phenoxy, halogen, halogenated alkyl, halogenated aryl, halogenated alkenyl, halogenated alkynyl, perhaloalkyl, perhaloaryl, a substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted cycloalkenyl ring, a substituted or unsubstituted saturated heterocyclic ring, a substituted or unsubstituted unsaturated heterocyclic ring, and at least one X is hydrogen, and when D is O, the position is not occupied;

Y_1 , Y_2 , Y_3 and Y_4 are the same or different and each is selected from the group consisting of



wherein:

Q is oxygen or ZR'

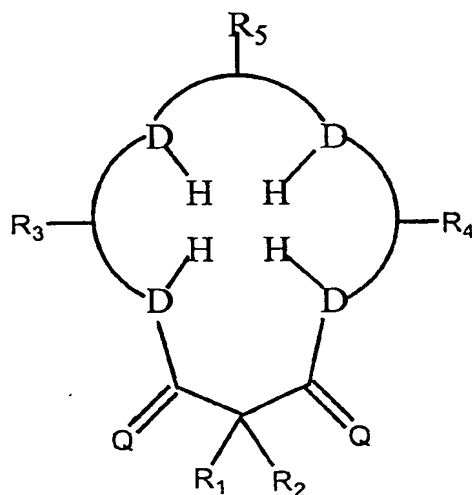
Z is selected from the group consisting of N, P and As; and,

- 5 R' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, phenoxy, halogen, halogenated alkyl, halogenated aryl, halogenated alkenyl, halogenated alkynyl, perhaloalkyl, perhaloaryl, a substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted cycloalkenyl ring, a substituted or unsubstituted saturated heterocyclic ring, a substituted or unsubstituted unsaturated heterocyclic ring;

R_5 , R_6 , R_7 and R_8 pairwise and cumulatively, are the same or different and each (i) is selected from the group consisting of alkyl, aryl, halogen, halogenated alkyls, halogenated aryls, CF_3 , CH_2CF_3 , cycloalkyl, cycloalkenyl, alkynyl, alkylaryl, alkoxy, phenoxy, oxylic, phenyl, or (ii) together with an R substituent on an adjacent carbon in the same Y unit, form a mono-, di-, tri- or tetra- substituted or unsubstituted benzene ring of which two carbons in the ring are adjacent carbons in the same Y unit, or (iii) together with a paired R bound to the same carbon atom form a substituted or unsubstituted cycloalkyl or substituted or unsubstituted cycloalkenyl ring.

R_1 and R_2 are the same or different, linked or nonlinked, and each is selected from the group consisting of substituents which are unreactive, form strong bonds intramolecularly with said R_1 and R_2 and with the carbon of the Y unit to which each is bound, are sterically hindered and are conformationally hindered such that oxidative degradation of a metal complex of the compound is restricted when the complex is in the presence of an oxidizing agent, or together with an R substituent on an adjacent carbon in the same Y unit, form a mono-, di-, tri- or tetra- substituted or unsubstituted benzene ring of which two carbons in the ring are adjacent carbons in the same Y unit.

Another embodiment of the compound of the invention is shown by the formula



(Compound 2)

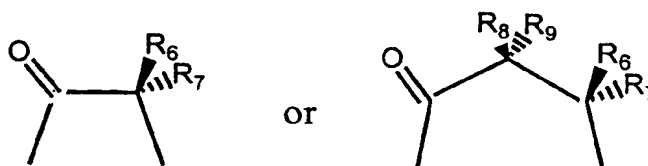
wherein R_1 and R_2 are the same or different, linked or nonlinked, and each is selected from the group consisting of substituents which are unreactive, form strong bonds intramolecularly

with said R_1 and R_2 and with the cyclic carbon to which each is bound, are sterically hindered and are conformationally hindered such that oxidative degradation of a metal complex of the compound is restricted when the complex is in the presence of an oxidizing agent. The low conformational freedom of the species prevents attainment of conformers that are conducive to intramolecular oxidative degradation.

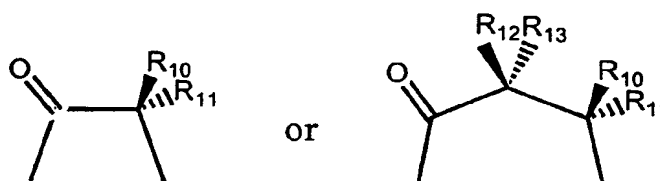
D is a donor atom, such as an oxidation resistant metal complexing atom, preferably N or O, bearing hydrogen where necessary.

Q is an oxidation resistant functionality, preferably O or NR_s wherein R_s is methyl, phenyl, hydroxyl, oxylic, $-CF_3$ or $-CH_2CF_3$.

R_3 is a unit joining the adjacent D atoms comprised of

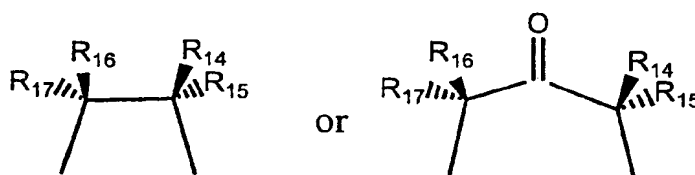


R_4 is a unit joining the adjacent D atoms comprised of



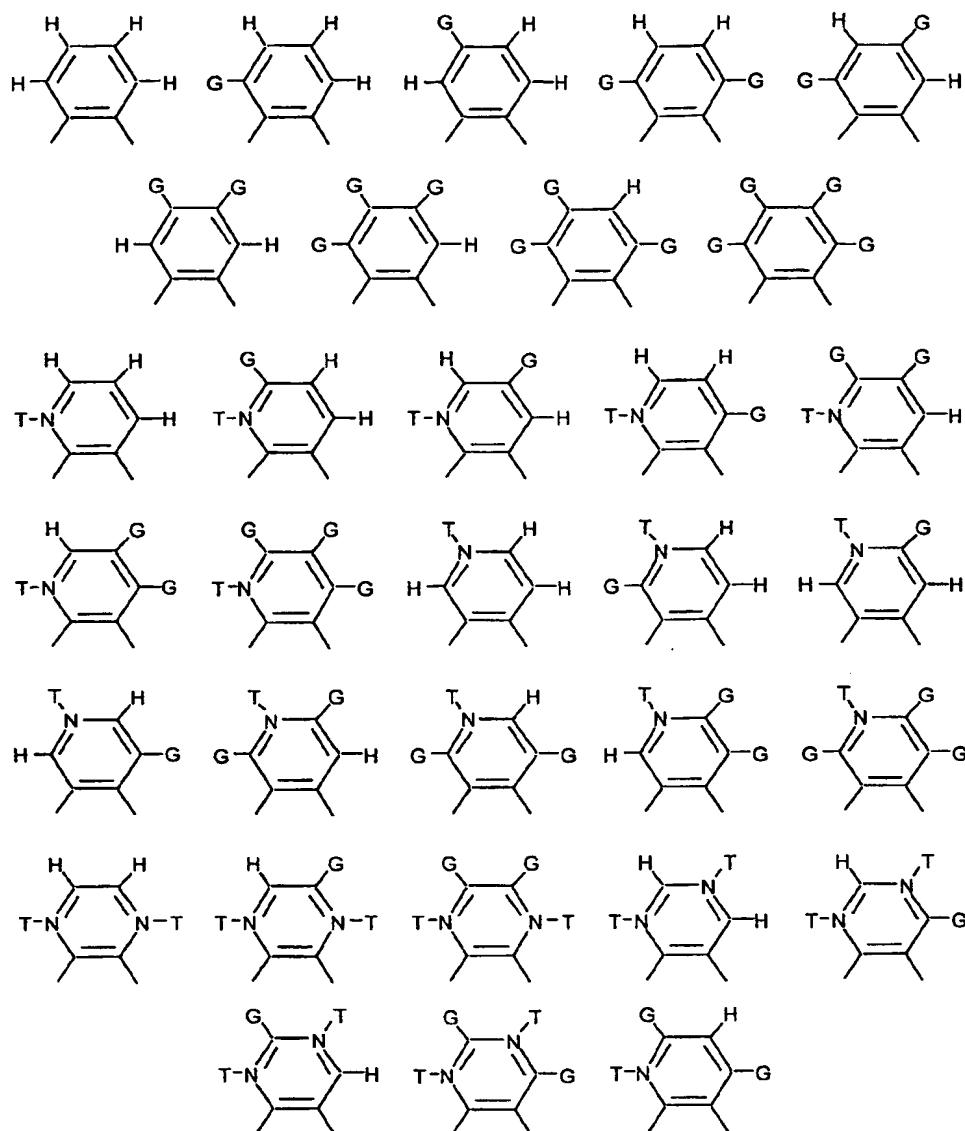
wherein R_6 and R_7 , R_8 and R_9 , and R_{10} and R_{11} , and R_{12} and R_{13} , pairwise and cumulatively, are the same or different and are selected from the group consisting of alkyl, aryl, hydrogen, halogens, CF_3 and combinations thereof; and

R_5 is a unit joining the adjacent D atoms comprised of: (i)



wherein R_{14} through R_{17} are the same or different and are alkyl, aryl, hydrogen, halogen, CF_3 or combinations thereof, or

(ii) an aryl group including



Each T in the foregoing benzene and substituted benzene structures is the same or different and may be an unoccupied position, or may be occupied with hydrogen, alkyl or haloalkyl.

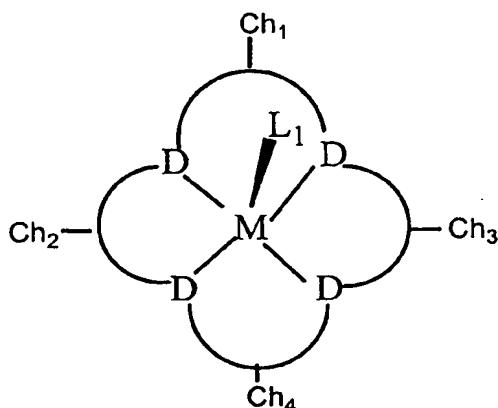
- 5 Each G is the same or different and comprises halogen, hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, alkylaryl, phenoxy substituents, amino, substituted amino, nitro, alkoxy, aryloxy and combinations thereof, or combine to form a cycloalkyl or cycloalkenyl ring, which may contain at least one atom that is not carbon. Two of the carbon atoms in the aryl group are bound to the nitrogen or oxygen in the tetradentate compound.

The present invention pertains to the novel changes to the macrocyclic structure that increase the robustness of tetra-aza macrocyclic ligands such that one can obtain ligand systems that can support catalysis based on purported highly reactive metal-oxo intermediates similar to those of the monooxygenases. The degradation chemistry that required the described changes was completely unexpected. Most significantly, the new systems described herein support catalysis with highly desirable O-atom transfer oxidants, especially peroxides, making them available for a wide range of technological oxidation applications where there is significant promise of obtaining chemically- and cost-effective catalyses.

Transition metal complexes of macrocyclic ligands have been used to catalyze oxidations in the past. Patented systems include porphyrins and phthalocyanines, halogenated porphyrins and ligands related to porphyrins, and substituted tricycloazanone and related macrocycles. All of these systems differ fundamentally from the system of the present invention in significant ways. First, the amide containing macrocyclic tetradentate compounds are tetraanionic and highly donating such that the ligands of the present invention render accessible the reactive high valent states of metals much better than any of the other macrocycles employed. Second, the macrocycles of the present invention can attain a high degree of protection with or without recourse to halogen substituents - the nonhalogenated species have a higher degree of environmental friendliness. Third, complexes of the amide containing macrocyclic compounds of the present invention exhibit a pronounced resistance to hydrolysis making them suitable for use in protic media, such as water, in which various metal ion salts are soluble.

The tetradentate macrocyclic compound of the present invention is designed to be complexed with a metal, preferably a transition metal chosen from Groups 3 through 12 of the Periodic Table, and most preferably a group 6 (Cr group), 7 (Mn group), 8 (Fe group), 9 (Co group), 10 (Ni group) or 11 (Cu group) transition metal, to form the corresponding chelate complex.

The invention therefore also includes a chelate complex of the formula



wherein M is a metal, D is a donor atom selected from the group consisting of N, O and NR_D , and R_D is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkoxy, phenoxy, halogen, halogenated alkyl, halogenated aryl, halogenated alkenyl, halogenated alkynyl, perhaloalkyl, perhaloaryl, a substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted cycloalkenyl ring, a substituted or unsubstituted saturated heterocyclic ring, and a substituted or unsubstituted unsaturated heterocyclic ring.

Ch_1 , Ch_2 , Ch_3 and Ch_4 are oxidation resistant components of the chelate system which are the same or different and which form five- to six-membered rings with the adjacent DMD atoms.

L_1 is an optional ligand. In the preferred embodiment, the axial ligand, L_1 , binds to the metal M. The ligand is labile because it occupies its position relative to the metal until the chelate system is introduced into a solution containing an oxidant. The labile ligand will dissociate in solution and will be replaced by the oxidant, most generally an O-atom transfer agent, but also any general oxidant that can serve to activate the metal ion to perform catalysis. Preferred labile ligands include the Cl^- anion, halide ions in general, CN^- , ROH , NH_3 , or any amine, carboxylate, phenol or phenoxide, nitrile, pyridine, ether, sulfoxide, ketone, or carbonate.

It has been determined that the oxidation site in iron complexes of aromatic ring-containing macrocycles (one electron oxidized above the Fe^{III} state) can be manipulated by choice of the axial ligands as well as by the aromatic ring substituents. Strong s-donor anionic axial ligands (CN^-) favor a metal-centered oxidation *i.e.*, Fe^{IV} , whereas weaker donors (e.g., Cl^-) favor a ligand-localized oxidation. The oxo intermediate form of the chelate

complex system is believed to function as the actual catalyst in some applications. In others, the chelate system can be the sole site of oxidation, or the oxidation site can be mixed between the chelate system, the metal and any other ligand attached to the metal.

5 The chelate groups Ch_1 , Ch_2 , Ch_3 , and Ch_4 correspond in composition to Y_1 , Y_2 , Y_3 , and Y_4 of compound 1 described above. Ch_1 may be the constituent described above as R_5 of the macrocyclic tetradentate compound 2. Ch_2 and Ch_3 correspond to the units R_3 and R_4 , respectively, of the macrocyclic tetradentate compound 2 described above.

10 Ch_4 corresponds to the linking constituent of compound 2 having the general formula $Q=CC(R'')_2C=Q$ wherein $(R'')_2$ is equivalent to R_1 and R_2 described above and Q is the oxidation resistant functionality described above.

R_1 and R_2 are key substituents in the design of the robust chelate complex and catalysts of the present invention. R_1 and R_2 are preferably methyl, CF_3 , hydrogen or halogen, or may form, together with the carbon atom to which both are bound, substituted and unsubstituted three-, four-, five- or six-membered ring, such as a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. It is believed that intramolecular reactions between the R_1 and R_2 substituents in prior art complexes and an oxo ligand in a functioning catalytic system contribute to the rapid degradation of the chelate ligand as has been heretofore experienced. See Fig. 1 for a proposed mechanism of oxidative degradation of the catalyst. It has been observed, for example, consistent with Fig. 1, that known catalyst compounds having diethyl substituents in the R_1 , R_2 positions are sensitive to oxidative attack such that, while catalytic oxidations can be observed, the ligand system simultaneously undergoes slow oxidative degradation. All of the tetraamide macrocycles described in the Collins, *Accounts of Chemical Research* article cited above include the diethyl substituents in the R_1 , R_2 positions. Thus, no macrocyclic tetraamide ligand transition metal complex has been shown heretofore to be competent to carry out useful oxidation catalyses by virtue of a significant longevity of the catalyst system.

The present invention also includes processes for the use of the complex defined above in the presence of an oxidant for performing of oxidation reactions. The complex may be present in substoichiometric amounts or in stoichiometric or near stoichiometric amounts.

30 The present invention also includes a process comprising exposing a target to an oxidant in the presence of the complex defined above. The oxidant may be halogen, halogen

oxide, halogenoxoanion, elemental halogen, a peroxy compound, such as hydrogen peroxide, oxygen, air, oxygen in the presence of an adjunct and combinations thereof. Alternatively, the oxidant may be chosen from elemental chlorine, chlorine oxide, chlorine oxoanion, chlorine dioxide, hypochlorite, acidic species thereof or combinations thereof.

- 5 In the process, the complex may be added for the purpose of activating the oxidant for sterilization, wound cleaning, fungicidal, bactericidal, insecticidal and herbicidal oxidations, or for sewerage and water treatment. The target may be a variety of organic or inorganic materials.

BRIEF DESCRIPTION OF THE FIGURES

- 10 FIG. 1 is a schematic illustration of the proposed path of oxidative ligand degradation of a catalyst system consisting of compound II and peroxides due to intramolecular reactions between a diethyl substituent and the oxo axial ligand;

FIG. 2 is an illustration of the manner in which conformational constraints prevent oxidative degradation of the oxo group;

- 15 FIGS. 3(a) and (b) are illustrations of two possible structures of the macrocyclic tetraamide ligand of the present invention showing the arm, linker and bridge components of the compound;

- FIG. 4 is a view of a recyclable metallo-oxidant system; FIG. 5 is a schematic view of an amino pendant macrocycle metal complex covalently bound to a support surface;
- 20 and

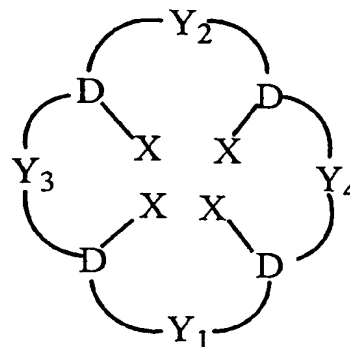
FIG. 6 is an illustration of several chelate complexes formed from the macrocyclic ligands of the invention.

- FIG. 7 is a graph showing the changes in the ultraviolet/visible spectrum that occur when thioflavin T, a basic yellow dye, is oxidized by H_2O_2 in the presence of the compounds
- 25 of the present invention.

FIG. 8 is a three dimensional graph showing the changes in the ultraviolet/visible spectrum that occur when Acid Yellow 54, an acidic dye, is bleached by H_2O_2 in the presence of the compound of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The preferred embodiment of the tetradentate macrocyclic compound of the present invention follows:



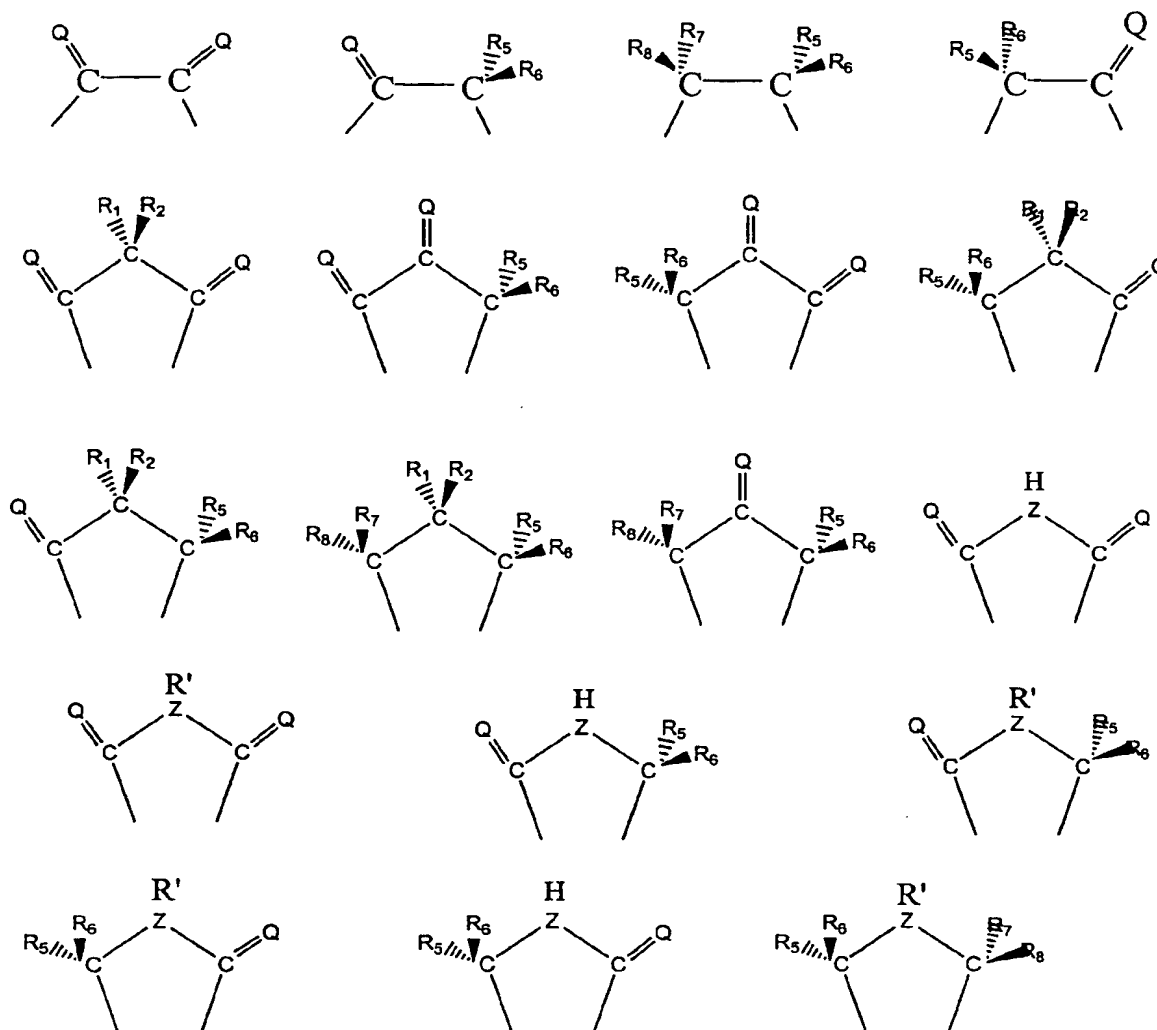
A macrocyclic tetradentate ligand having the structure

5 wherein:

D is a donor atom selected from the group consisting of N and O;

each X is a position for addition of a substituent and, when D is N each position is (i) not occupied such that a double bond is formed between D and an atom adjacent to D, or (ii) is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, phenoxy, halogen, halogenated alkyl, halogenated aryl, halogenated alkenyl, halogenated alkynyl, perhaloalkyl, perhaloaryl, a substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted cycloalkenyl ring, a substituted or unsubstituted saturated heterocyclic ring, a substituted or unsubstituted unsaturated heterocyclic ring, and at least one X is hydrogen, and when D is O, the position is not occupied;

15 Y₁, Y₂, Y₃ and Y₄ are the same or different and each is selected from the group consisting of



wherein:

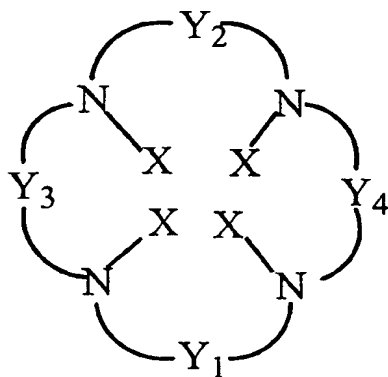
Q is oxygen or ZR';

- 5 Z is selected from the group consisting of N, P and As; and, R' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, phenoxy, halogen, halogenated alkyl, halogenated aryl, halogenated alkenyl, halogenated alkynyl, perhaloalkyl, perhaloaryl, a substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted cycloalkenyl ring, a substituted or unsubstituted saturated heterocyclic ring, a substituted or unsubstituted unsaturated heterocyclic ring.
- 10 R₅, R₆, R₇ and R₈ pairwise and cumulatively, are the same or different and each (i) is selected from the group consisting of alkyl, aryl, halogen, halogenated alkyls, halogenated

aryls, CF_3 , CH_2CF_3 , cycloalkyl, cycloalkenyl, alkynyl, alkylaryl, alkoxy, phenoxy, oxylic, phenyl, or (ii) together with an R substituent on an adjacent carbon in the same Y unit, form a mono-, di-, tri- or tetra- substituted or unsubstituted benzene ring of which two carbons in the ring are adjacent carbons in the same Y unit, or (iii) together with a paired R bound to the same carbon atom form a substituted or unsubstituted cycloalkyl or substituted or unsubstituted cycloalkenyl ring;

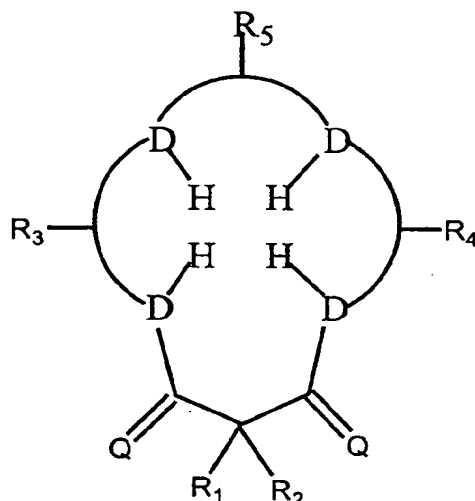
R_1 and R_2 are the same or different, linked or nonlinked, and each is selected from the group consisting of substituents which are unreactive, form strong bonds intramolecularly with said R_1 and R_2 and with the carbon of the Y unit to which each is bound, are sterically hindered and are conformationally hindered such that oxidative degradation of a metal complex of the compound is restricted when the complex is in the presence of an oxidizing agent, or together with an R substituent on an adjacent carbon in the same Y unit, form a mono-, di-, tri- or tetra- substituted or unsubstituted benzene ring of which two carbons in the ring are adjacent carbons in the same Y unit.

The preferred embodiment of compound 1 has the structure



wherein each D is N. The remaining substituents are as described above.

Another embodiment of the macrocyclic compound of the present invention, Compound 2, differs from compound 1 in that a carbon atom occupies the position of the heteroatom Z shown above, has the structure:

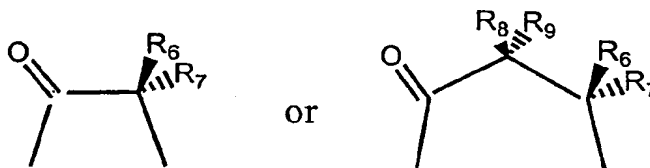


wherein:

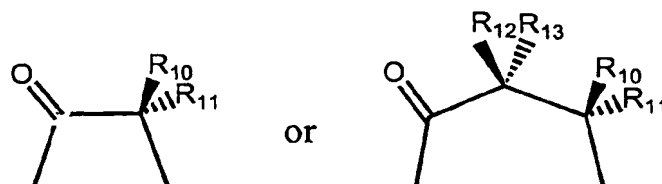
R_1 and R_2 are the same or different, linked or nonlinked, and each is selected from the group consisting of substituents which are unreactive, form strong bonds intramolecularly with said R_1 and R_2 and with the carbon of the Y unit to which each is bound, are sterically hindered and are conformationally hindered such that oxidative degradation of a metal complex of the compound is restricted when the complex is in the presence of an oxidizing agent. The low conformational freedom of the R_1 and R_2 species prevents attainment of conformers that are conducive to intramolecular oxidative degradation.

D is a donor atom, such as an oxidation resistant metal complexing atom, preferably N or O, bearing H where necessary. Preferably at least three D's are N. Q is an oxidation resistant functionality, preferably O or NR_x wherein R_x is alkyl, aryl, halogenated alkyl, halogenated aryl, methyl, phenyl, hydroxy, oxylic, $-CF_3$ or $-CH_2CF_3$.

R_3 is a unit joining the adjacent Z atoms comprised of

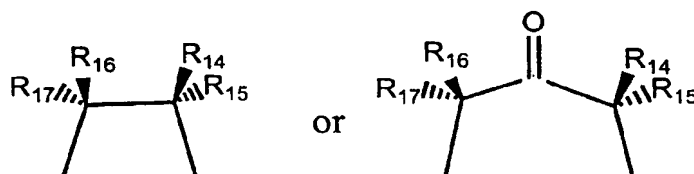


R_4 is a unit joining the adjacent D atoms comprised of



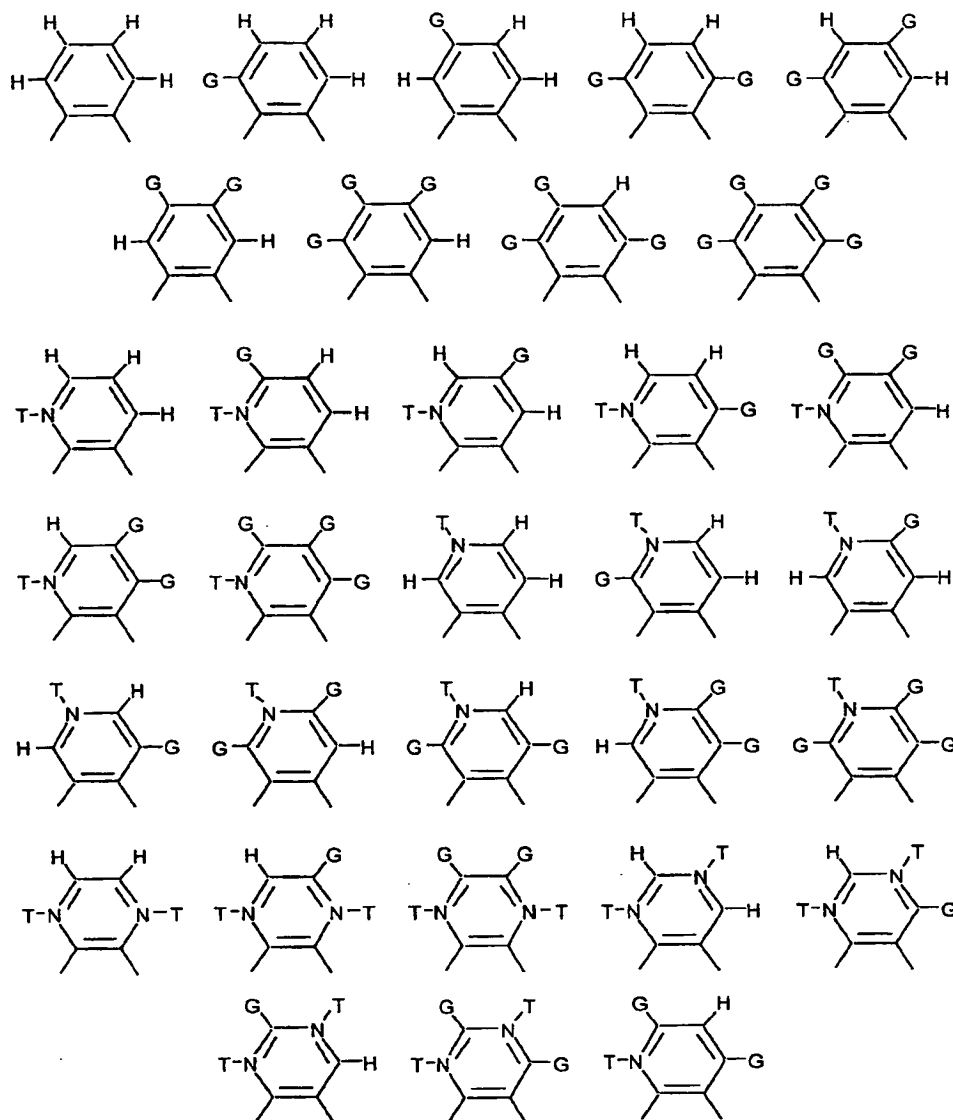
wherein R_6 and R_7 , R_8 and R_9 , and R_{10} and R_{11} , and R_{12} and R_{13} , pairwise and cumulatively, are the same or different and are selected from the group consisting of alkyl, aryl, hydrogen, halogens, CF_3 , and combinations thereof; and

- 5 R_5 is a unit joining the adjacent D atoms comprised of: (i)



wherein R_{14} through R_{17} are the same or different and are alkyl, aryl, hydrogen, halogen, CF_3 , or combinations thereof, or

- (ii) an aryl group including



Each T in the foregoing benzene and substituted benzene structures is the same or different and may be an unoccupied position, or may be occupied with hydrogen, alkyl or haloalkyl.

- 5 Each G is the same or different and comprises halogen, hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, alkylaryl, phenoxy substituents, amino, substituted amino, nitro, alkoxy, aryloxy and combinations thereof, or combine to form a cycloalkyl or cycloalkenyl ring, which may contain at least one atom that is not carbon. Two of the carbon atoms in the aryl group are bound to the nitrogen or oxygen in the tetradentate compound.

The compounds of the present invention form robust, long-lived oxidation catalysts and precatalysts. For the sake of convenience, and without limiting the scope of the invention, "catalyst" will be used herein to include precatalysts and actual catalyst complexes, where the latter is the species that carries out the oxidation. In many cases, the precise catalytic mechanism is not known and thus the precise role in any given oxidation reaction of the chelate system and compounds of the present invention may not be known. The compounds may function as activators for initiation of the catalytic reaction. As used herein, robust oxidation catalyst means that when the catalyst is added to a solvent in the presence of an oxidant, such as a peroxide or any oxygen transfer agent, the half-life of the activated form of the metal complex is 30 seconds or more. The half-life is the time in which half of the metal complex decomposes or degrades.

Surprisingly, the design of one of the most preferred embodiments of the new robust compounds differs from the prior art compounds by only one constituent. By changing the R_1 , R_2 diethyl substituents of the prior art tetraamido compounds to dimethyl substituents, the previously fragile, short-lived chelate complexes are transformed unexpectedly into stable, long-lived complexes which are very resistant to oxidative degradation. What appeared to be a minor change in the structure is in fact the key to a new class of robust long-lived oxidation catalysts. The C-H bond strength of the methyl substituent is about 3 Kcal.mol⁻¹ greater than the C-H bond strength of the corresponding ethyl substituent. It has been determined that any R_1 , R_2 substituents which are unreactive, or which form strong bonds with the cyclic carbon, or are sterically or conformational hindered, such that they are restricted from intramolecular reaction with the axial oxo ligand will also form the robust catalysts, or precatalysts of the invention.

The importance of the bond strength and/or conformational constraints can be seen from the following determinations. In order to support oxidation catalysis, every component of the ligand system must be substantially resistant to oxidative degradation. The key to the stability of the R_1 and R_2 groups has been determined by observation in a particularly informative case. As shown in Fig. 1, iron (III) aqua complexes react with hydroperoxides to give a purported oxo complex which it has been shown exhibit catalytic properties for the oxidation of nitriles containing C-H bonds α to the cyano group. However, as catalysis proceeds the ligand system slowly decomposes and it is proposed that this degradation

proceeds via abstraction of an H-atom from a methylene group of an ethyl substituent in the R_1 position as is consistent with the structure of the hydantoin-ring containing degradation product, labeled III (Fig. 1). Molecular models reveal that a highly strained conformation of the CH_4 -containing chelate ring is required to bring the abstractable H-atom close to the abstracting O-atom. Compound III has been unambiguously characterized by a variety of mass spectrometric, 1H and ^{13}C NMR, IR, elemental analyses. Simultaneously with the observed degradation, the system catalytically oxidizes the weakest C-H bond in a series of nitriles [$(CH_3)_2CHCN$, CH_3CH_2CN , CH_3CN , CD_3CN] which are employed as solvents. The products are mixtures of nitrile oxidation products. Thus, where t-butyl hydroperoxide is the primary oxidant, the product mixture with $(CH_3)_2CHCN$ as the substrate contains $(CH_3)_2C(OH)CN$, $(CH_3)_2(CN)COOC(CH_3)_3$, $(CH_3)_2(CN)COOCH_3$, $(CH_3)_2C=O$, $(CH_3)_3COH$. It has also been shown that while this product mixture suggests a free radical autoxidation process where the role of the iron complex, II (Fig. 1), would be to initiate the process, free radical autoxidation cannot be the dominant mechanism. Thus, when the oxidation is carried out under $^{18}O_2$ (1 atm, > 98%) the yield of $^{18}O_2$ labelled products is too low for the reaction mechanism to be consistent with a completely free radical autoxidation process. By replacement of CH_3 - for CH_3CH_2 - in the R_1 and R_2 positions, the ligand degradation is dramatically suppressed such that nitrile oxidation alone dominates the oxidative reactivity. This inhibition of ligand degradation by the CH_3 - for CH_3CH_2 - can be rationalized as resulting from the increased C-H bond strength of CH_3 - versus CH_3CH_2 -, ca. 3 kcal/mol $^{-1}$, thereby slowing the rate of the H-atom abstraction by the oxo ligand by ca. three orders of magnitude. Since it is apparent that the abstraction is critical to the degradation, the orientation of the abstractable H-atom with respect to the oxo ligand is also critical as this orientation determines the distance of approach and abstraction reactions are exquisitely distance dependent. Molecular models reveal that if a cyclopentyl unit is employed to replace the ethyl groups of R_1 and R_2 , the methylenic C-H group equivalent to that abstracted from the ethyl C-H group cannot reach the oxo ligand without considerably more ring-strain than that found in the ethyl case. Thus, the conformational constraint approach serves to dramatically increase the resistance of a so-substituted chelate to oxidative degradation.

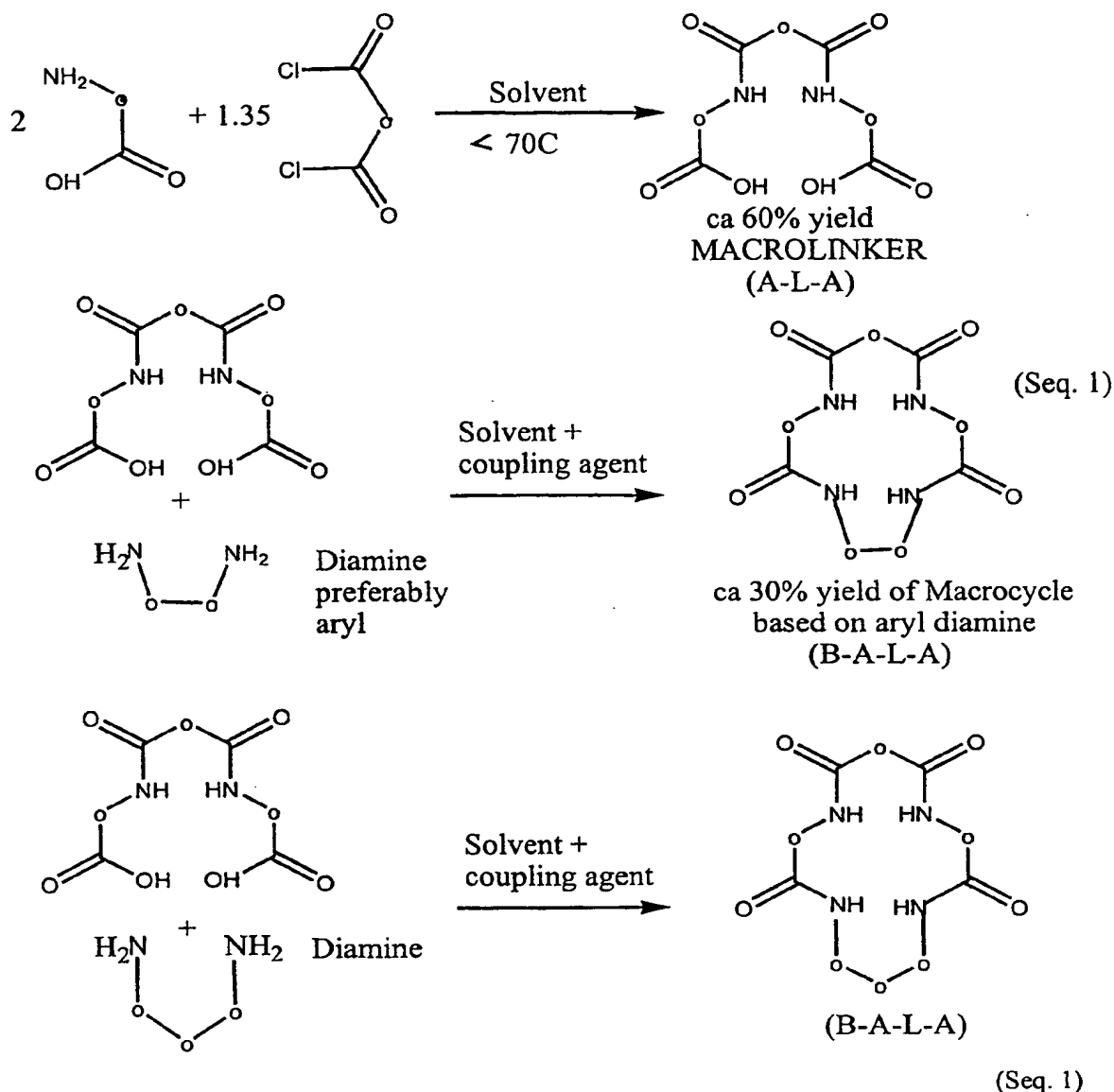
In the structure shown in Fig. 2, the oxo group and methylenic H are restricted from as close an approach as in the ethyl case because the methylene group of the cyclopentyl substituent cannot rotate freely to bring the two groups into as close a juxtaposition.

The compounds of the present invention are macrocyclic donor ligands which can be complexed with a metal and axial ligand to form the chelate/catalyst system of the present invention. The preferred design for producing robust ligands is an amide containing macrocyclic ligand having at least one amide and no hydrogens α to N-amido donor group or groups. When coordinated with the metal ion, five- and six-membered chelate rings are most stable. The substituents can vary considerably provided they meet the requirements described above. This is particularly critical for the R_1 and R_2 substituents.

An azide based synthetic route to macrocyclic tetraamido ligands is described in Uffelman, E.S., Ph.D. Thesis, California Institute of Technology, (1992). Alternatively, and preferably, the compounds of the present invention can be synthesized by a new synthetic route, described in co-pending U.S. patent application Serial No. 08/681,187 of S.W. Gordon-Wylie et al., entitled "Synthesis of Macrocyclic Tetraamido-N Ligands", filed on July 22, 1996, the disclosure of which is incorporated herein by reference.

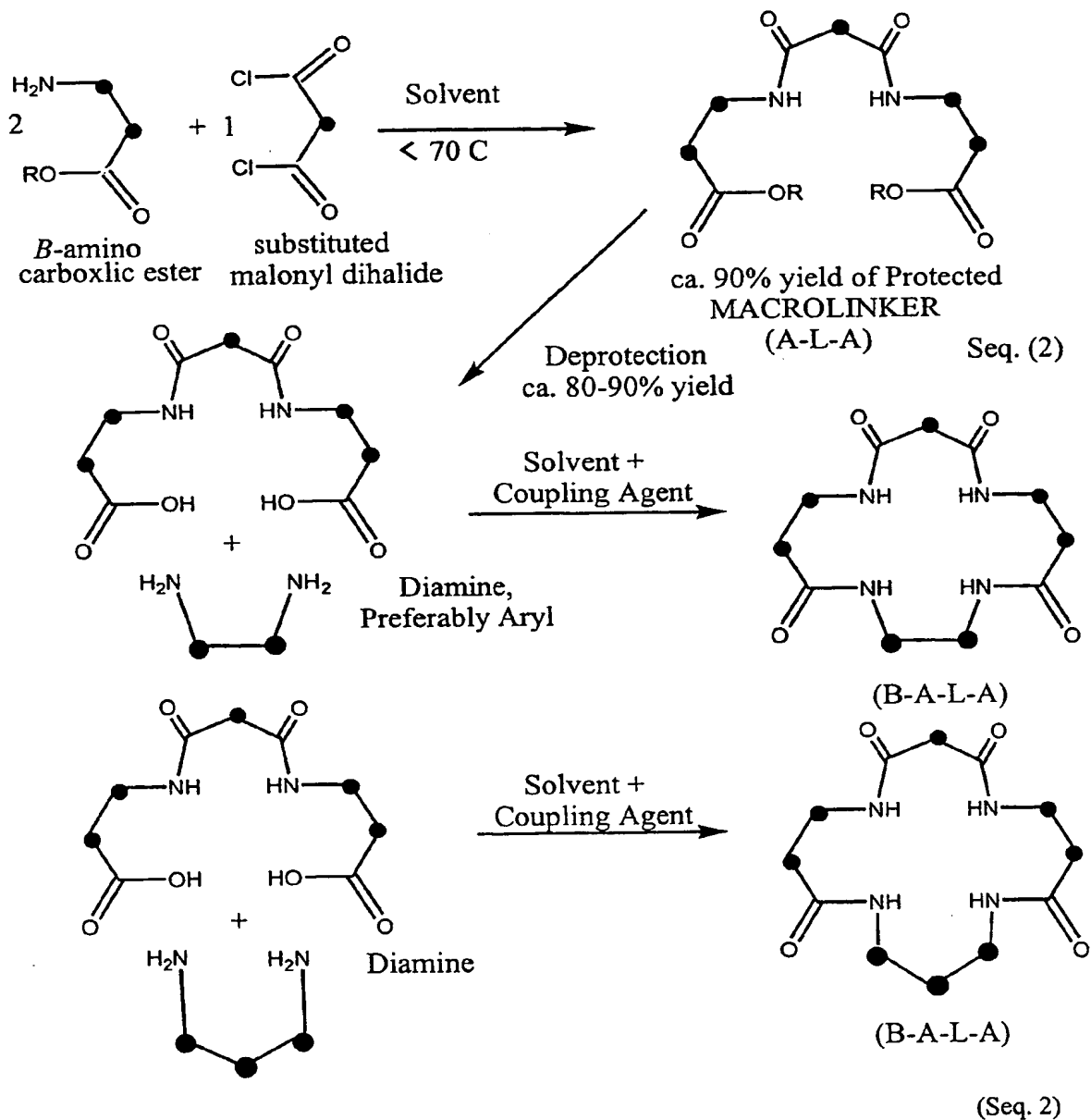
The new synthesis method permits the synthesis of variants which cannot be synthesized via the prior art azide based method. In varying the macrocycle, however, it is important to preserve the general framework of the compound. The macrocycle will be made up of 5- and 6-membered chelate rings, in a 5,5,5,5 pattern, a 5,5,5,6 pattern, a 5,6,5,6, pattern, a 5,6,6,6 pattern, or a 6,6,6,6 ring pattern discussed in more detail below.

The new synthetic method proceeds generally as shown in sequences 1 and 2 below. Specific examples of the application of the new method to the synthesis of some particular amide containing macrocycles are shown in sequence 3. For convenience of classification herein, the starting materials that are composed of diamine functionalities are sometimes referred to as "Bridges" (B), the starting materials composed of diacid functionalities are sometimes referred to as "Linkers" (L), and the starting materials composed of amine/acid functionalities are sometimes referred to as "Arms" (A). See Figs. 3(a) and (b). The arms of the macrocyclic compound are far more robust than the linker and are resistant to degradative attacks.



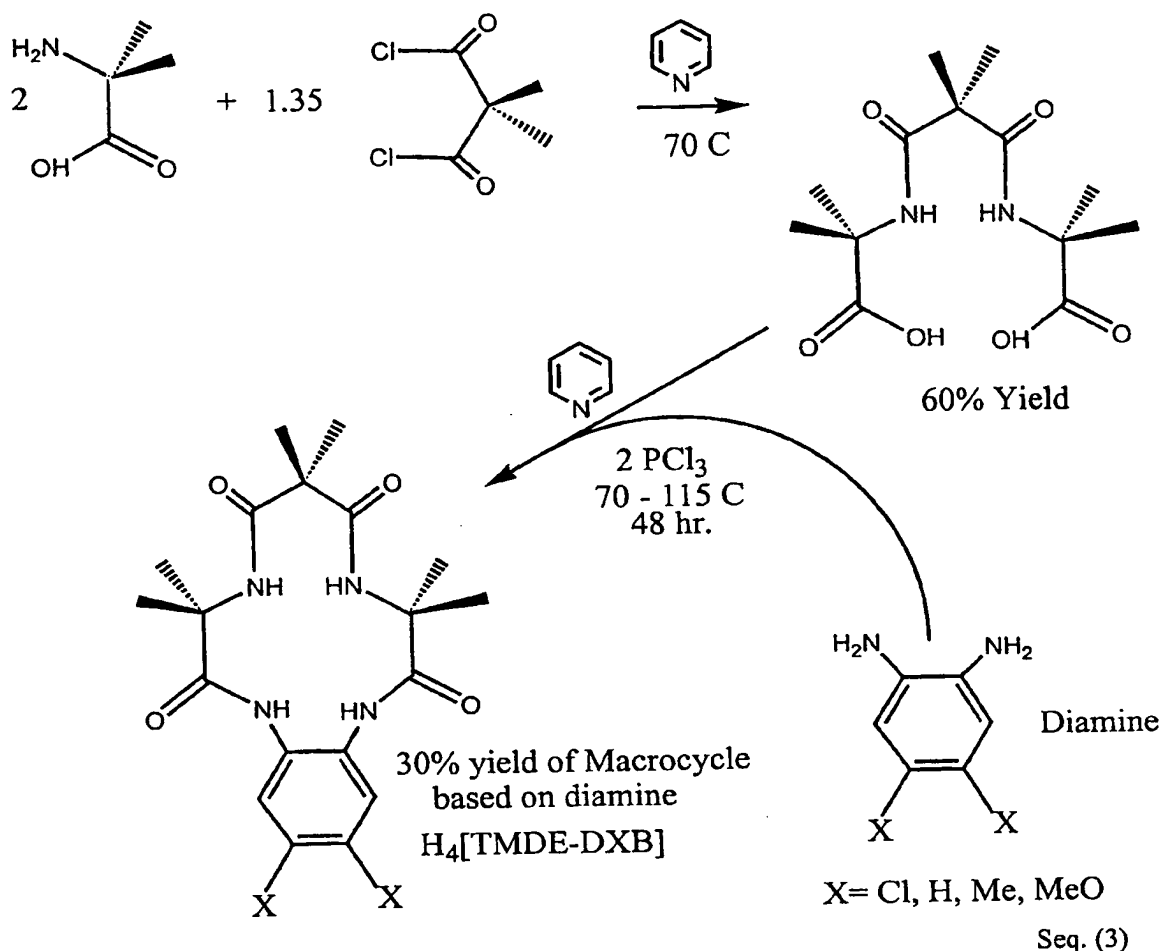
Sequence 1 is a generalized synthesis of amide containing tetradentate macrocycles having a (B-A-L-A-) configuration, from α -amino carboxylic acids via the new synthetic method. A diamide dicarboxyl-containing intermediate, sometimes referred to herein by the short hand designation, "macro linker intermediate" or simply the "intermediate" (A-L-A) is preformed without the use of protecting groups via a selective double coupling reaction wherein an α -amino carboxylic acid, the arms, A, and an activated malonic acid derivative, the linker, L, in solvent are heated to form the macro linker intermediate. The macro linker intermediate is

then coupled to a diamine, the bridge, B, in another selective double coupling reaction that employs a solvent, a coupling agent and heat. The synthetic methodology is highly streamlined and tolerates a wide range of functional groups. A wide range of amide containing tetradentate macrocycles bearing different electronic or steric substituents have
 5 been prepared in this manner in good yield.



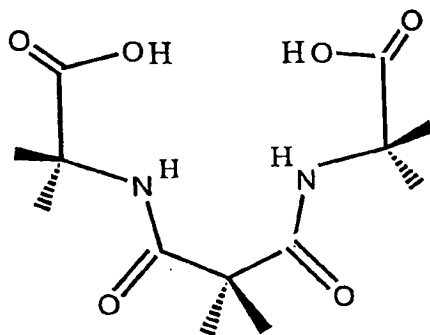
Sequence 2 is a generalized synthesis of an amide containing tetradentate macrocycle having a (B-A-L-A-) configuration, from b-amino carboxylic acids via a modified version of the basic, or primary, synthetic method. The basic approach employed with a-amino carboxylic acid starting materials is applied to b-amino carboxylic acid starting materials. For some b-amino carboxylic acids, use of a protecting group may be desirable, as shown in Sequence 2. A macro linker intermediate (A-L-A) is preformed via a selective double coupling reaction wherein a protected b-amino carboxylic ester arm, A, and an activated malonic acid derivative linker, L, in solvent are heated to form the intermediate, which, after deprotection, can then be coupled to the diamine bridge, B, in another selective double coupling reaction to yield a wide variety of substituted amide containing macrocyclic tetradentates with an expanded ring size compared to those that have been prepared from a-amino carboxylic acids.

The macro linker intermediate (A-L-A) can be made on a large scale in batch or continuous processing via direct reaction of a substituted malonyl dihalide with a solution (preferably a pyridine solution) of an a or b-amino carboxylic acid or ester. Many examples of the reaction proceed in good yield without protecting groups at temperatures preferably less than or equal to about 70°C. Some examples may require the use of protecting groups and these reactions generally proceed in good yield. The intermediate can be separated into batches and each separate batch further reacted with a wide range of diamine bridging compounds having different steric or electronic substituents in the presence of a coupling agent. For the a-amino carboxylic acid case, the ring closing step proceeds for 48-120 hours and is ideally substantially moisture free. See Sequence 3. A wide range of amide containing macrocycles having finely tuned electronic properties can be synthesized at a considerable cost savings over the prior art azide method.



Sequence 3 is a specific example of the preparation of a macrocyclic tetraamide having a (B-A-L-A-) configuration from α -amino carboxylic acid starting materials. An α -amino carboxylic acid is mixed with an activated malonate in pyridine at temperatures less than 70°C. After the selective double coupling reaction is complete, 72-144 hrs, the macro linker intermediate (A-L-A) is isolated. In a second step a diamine, preferably an o-phenylene diamine, is added to a pyridine solution of the macro linker intermediate in the presence of a coupling agent, preferably PCl_3 or pivaloyl chloride. The ring closure, a double coupling reaction, is allowed to proceed at reflux for 48-110 hrs, and then the desired amide containing macrocycle is isolated in good yield.

The synthesis of oxidatively robust macrocyclic tetradentates requires that all H atoms a to the donor atoms be replaced by more oxidatively robust groups such as alkyl, halo, aryl or heterocyclic substituents.



Structure 1

5

Structure 1 shows the key intermediate in the production of the catalyst of the present invention, an oxidatively robust macro linker (Arm-Linker-Arm). This molecule can be readily synthesized in one step without the use of protecting groups via the direct acylation of a-methylalanine with dimethyl malonyl dichloride.

10 In an alternative embodiment, the method of the invention uses protection/deprotection sequences to generate a protected form of the macro linker intermediate. Upon deprotection, the intermediate is coupled via the double coupling reaction described above to generate the amide containing macrocycle. Similarly, protection/deprotection sequences can be applied to substituents present on the bridging unit
15 to expand the range of bridging substituents that can be utilized in the macrocyclization reaction.

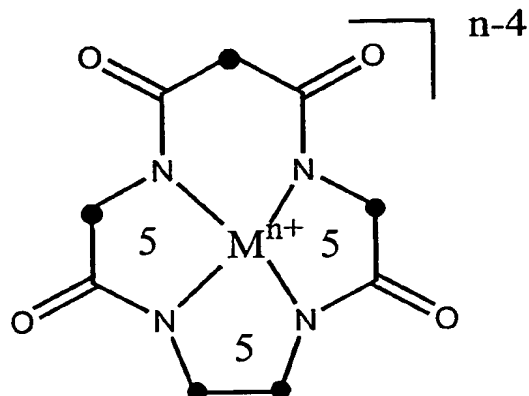
Both embodiments of the method of the invention rely heavily on the amine and carboxylic acid based starting materials hereinafter listed in Table 1. Table 1 lists several forms of the starting materials in what is designated the parent, protected/activated and
20 hidden forms of the amine and carboxylic acid functionalities in a general sense. Table 2 utilizes these categories in conjunction with chelation ring size constraints (5- and 6-membered chelate rings are preferred) in order to identify useful starting materials for the synthesis of chelating amide containing macrocyclic tetradentate compounds having the desired five- or six-membered ring.

As used herein "parent groups" (shown in *italics* in Table 1) define a preferred synthetic functionality. "Protected/activated groups" refers to those groups that contain an easily recognizable portion of the parent group. "Hidden groups" as used herein refers to those groups that need not contain an easily recognizable portion of the parent group but which are capable of ready conversion to the parent group or to a protected/activated form of the parent group. More detailed examples may readily be found in Greene and Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York (1981). An extensive list of protecting/activating groups particularly suitable for peptide synthesis may be found in G. A. Fletcher and J. H. Jones, "A List of Amino-Acid Derivatives Which are Useful in Peptide Synthesis", Int. J. Peptide Protein Res. 4, (1972), p.347-371.

WO 99/64156

		<u>Table 1</u>	
		Protected/ Activated	Hidden
		Carboxylic Acids	Carboxylic
5	Protected/ Activated Amines Acids	Hidden Amines	
10	N-alkyl amines amides amino acetals N-benzyls carbamates enamines hydrazines	azides azo compounds imides isocyanates isothiocyanates nitriliumions nitro compounds phosphazos	activated esters acyl halides amides anhydrides hydrazides O-acyl oximes oxazolidines oxazolones phosphite esters silyl esters stannyl esters
15	imines N-oxides N-phosphinyls N-phosphoryls N-Metal		nitriles oxazolines
20	derivatives silyl amines (N-Si) N-Sulphenyls sulfonamides N-Sulfonyls		substituted benzyl esters substituted ethyl esters substituted methyl esters sulfonyl esters sulphenyl esters
25	urea derivatives		

Structure 2 is used herein to define the shorthand notation shown in Table 2 and Table 3 that specifies the chelate ring sizes (including the metal ion) that are formed when a given macrocyclic ligand is coordinated to a transition metal center.



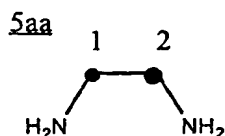
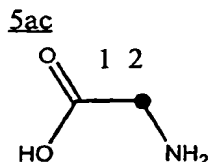
Structure 2

Amine is designated by "a", and carboxylate by "c".

Dashes (-) indicate amide bonds. Every dash must connect a trailing "a" to a leading "c" or vice versa, the final dash wraps around to the beginning. Structure 2 illustrates a (5,5,6,5) macrocyclic ligand shown in metal coordinated form with chelate ring sizes (including the metal ion) indicated. Using a counterclockwise rotation, the specific macrocycle employed is 5aa-5ca-6cc-5ac- (or any cyclic permutation thereof).

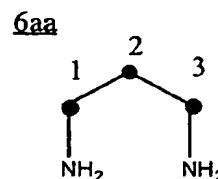
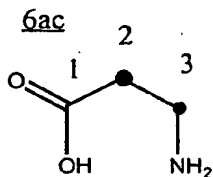
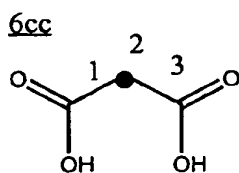
The parent (=) forms of the functional groups for each starting material are shown pictorially in Table 2 below, while possible combinations of protected/activated (p/a) or hidden (h) forms for each starting material are shown in tabular form. Variable positions are marked with a bullet (*). The underlined side captions are in a shorthand notation that refers to chelation ring sizes formed when the particular starting material is incorporated into a macrocycle and coordinated to a metal center. (See Structure 2)

Table 2



C ₁	2-N	C ₁	2-N	C ₁	2-N
=	=	p/a	=	h	=
=	p/a	p/a	p/a	h	p/a
=	h	p/a	h	h	h

C ₁	2-N	C ₁	2-N	C ₁	2-N
=	=	p/a	=	h	=
=	p/a	p/a	p/a	h	p/a
=	h	p/a	h	h	h



C ₁	C ₃	C ₁	C ₃	C ₁	C ₃
=	=	p	=	h	=
=	p/a	p/a	p/a	h	p/a
=	h	p/a	h	h	h

C ₁	3-N	C ₁	3-N	C ₁	3-N
=	=	p/a	=	h	=
=	p/a	p/a	p/a	h	p/a
=	h	p/a	h	h	h

1-N	3-N	1-N	3-N	1-N	3-N
=	=	p/a	=	h	=
=	p/a	p/a	p/a	h	p/a
=	h	p/a	h	h	h

The complete range of amide containing macrocyclic compounds able to be synthesized from the starting materials identified in Table 2 and those that can be generated according to the procedures discussed below is shown in general terms in Table 3.

5 3. Each unique combination has been listed pictorially and labelled with the shorthand notation of Structure 2 defined above.

The individual Bridge, Arm and Linker starting materials can either be obtained commercially or synthesized by standard techniques. Examples of syntheses for a few noncommercially available starting materials are provided herein and in the Experimental

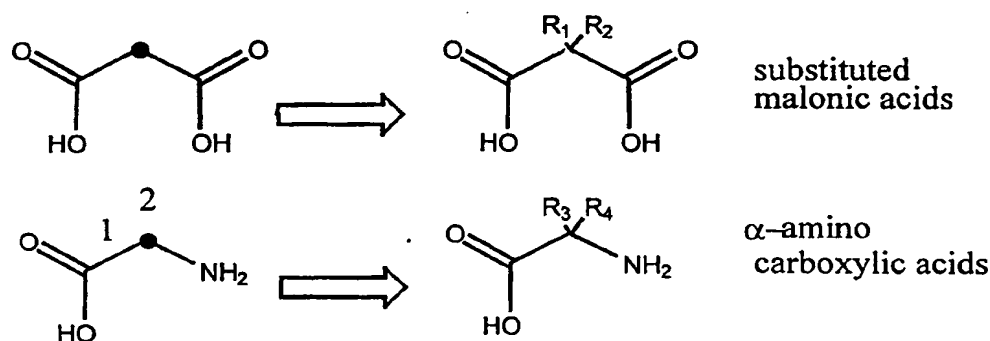
10 Section. A powerful alternative route for the preparation of substituted and unsubstituted malonates has been reported by A. P. Krapcho, E. G. E. Jahngen, Jr. and D. S. Kashdan. "α-carbalkoxylations of carboxylic acids. A general synthetic route to monoesters of malonic acids", Tet. Lett. 32, p. 2721-2723 (1974). The oxidatively robust amide

15 containing macrocycles shown in Table 3 may be synthesized without having to resort to the use of species that contain high energy N-N bonds, such as azides, hydrazines and azo constituents.

Schematics 1 to 3 below pictorially demonstrate substitution at the variable positions shown in Table 3. The remainder of this section discusses how to choose R substituents in general terms, and lists some representative examples of substituted Bridge, Arm and Linker starting materials in tabular form.

5 Single Node Substitution

Starting materials containing only one variable position are substituted by a carbon atom bearing two R groups, a $-C(R_a)(R_b)-$ unit, (in this context the dashes (-) refer to single bonds as opposed to amide bonds).



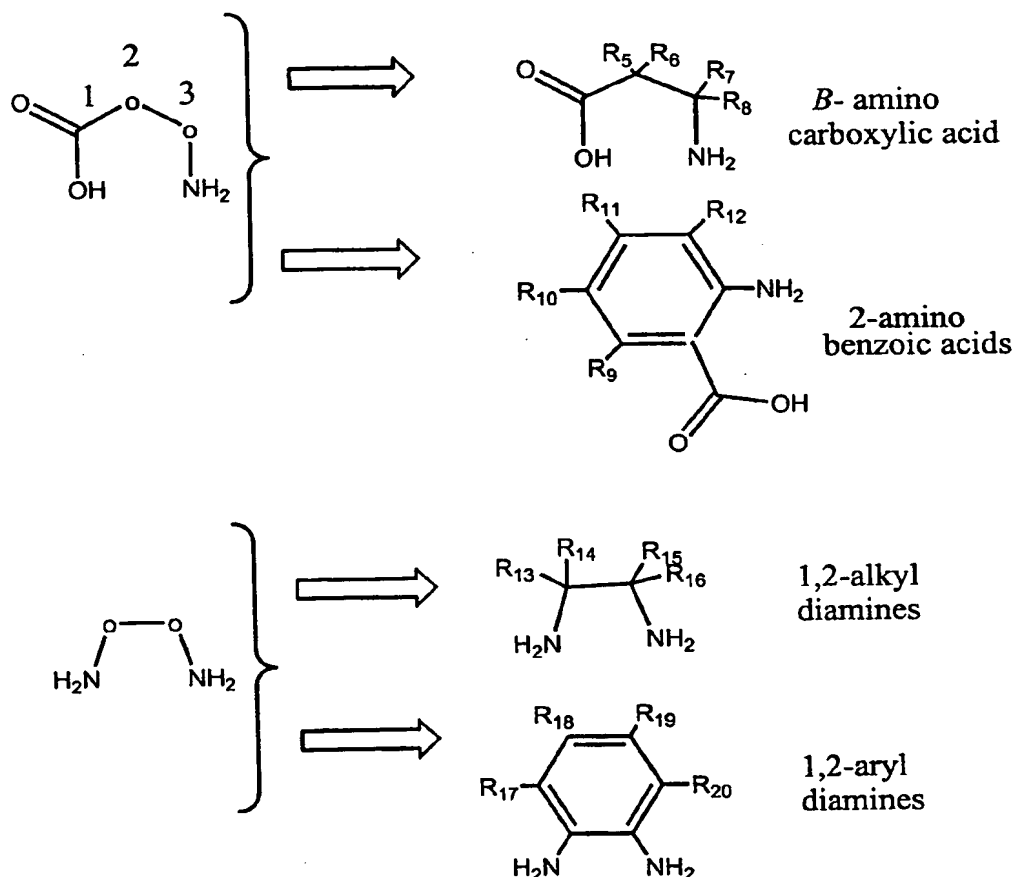
10

Schematic 1: Replacement of a single variable position is always by a $-C(R_a)(R_b)-$ unit.

For substitution at any single variable position the R groups on the $-C(R_a)(R_b)-$ unit may be the same or different and are selected from the group consisting of hydrocarbons and heteroatom (e.g., halogen, N, O, Si, P, S) substituted hydrocarbons. Specific choices for the R groups other than R_1 and R_2 are from the following types/subtypes either singly or in combination (e.g. for R = arylsilylester, only aryl, esters and siloxanes are listed); H, ketones, aldehydes, carboxylic acids, hidden or protected/activated carboxylic acids (*see* Table 1), esters, ethers, amines, hidden or protected/activated amines (*see* Table 1), imines, amides, nitro, sulphonyls, sulfates, phosphoryls, phosphates, silyl, siloxanes, alkyl, alkenyl, alkynyl, halo, aryl, and compounds chosen from biological systems e.g. natural or unnatural amino acid sidechains, heterocyclic rings, lactams, lactones, alkaloids, terpenes (steroids, isoprenoids), lipid or phospholipid chains. For single node substitution, fusion of the R_a and R_b groups at a position that is not the site of substitution, but a to the site of substitution yields a species doubly bonded to the node such as an oxo ($=O$), imine ($=NR_a$), or a substituted vinyl group ($=CR_aR_b$). Formation of imines or substituted vinyl groups constitutes a form of nodal

migration. If the original R_a and R_b groups are fused at a site that is not the site of substitution and is not a to the site of substitution then a cyclic ring structure is formed. If such cyclic groups are formed, additional R substituents on the cyclic groups are chosen in the same manner as for normal single node or multi node substitution (including the possibility of

5 further R group fusions at one or more nodes to yield additional oxo, imine, substituted vinyl groups, or spiro, benzo, substituted benzo, heterocyclic, substituted heterocyclic, cycloalkyl, substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl ring structures). Preferred spiro/cyclic ring sizes are three-, four-, five- or six- membered rings.

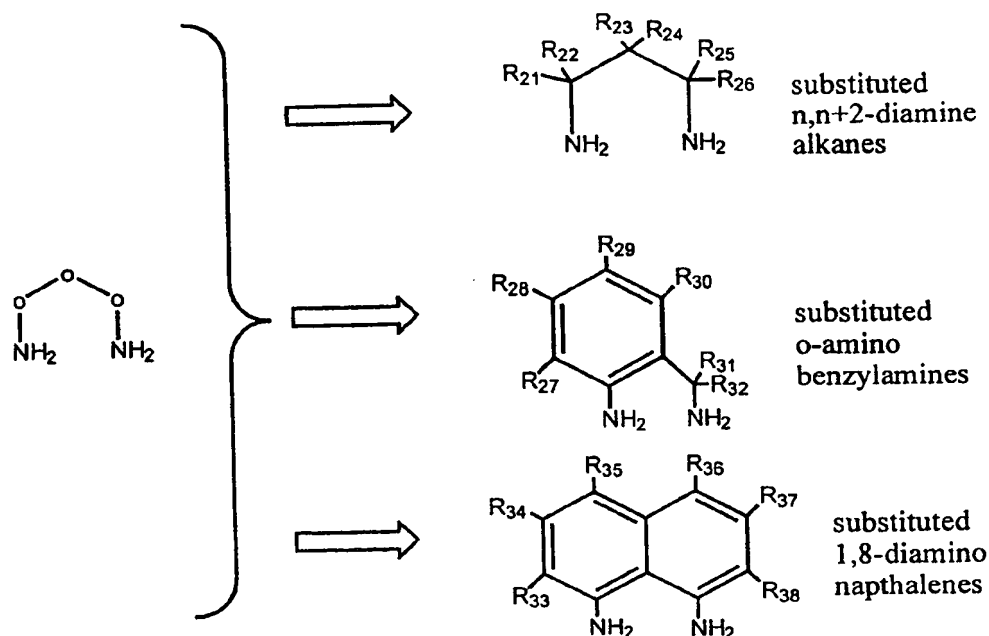
Multi Node Substitution

Schematic 2: Replacement at two variable positions can be by two $-C(R_a)(R_b)-$ units or the two variable positions can be combined to make up part of an aryl or heterocyclic ring structure. For multiple node substitution individual $-C(R_a)(R_b)-$ positions are substituted identically as for single node substitution (*see above*). In addition to the types of substitution found for single nodes, it is also possible to combine or connect multiple nodes together via fusion of the R groups located on different nodes at sites that either are (combination), or are not (connection), the sites of attachment. Combination of sites that are adjacent leads to ethylenic units ($-C(R_a)=C(R_b)-$) a form of R group elimination. Connection of nodes via R

group fusion at sites that are not the points of attachment or combination of sites that are not adjacent leads to the formation of cyclic structures, such as spiro, benzo, substituted benzo, heterocyclic, substituted heterocyclic, cycloalkyl, substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl ring structures. Five- and six-membered rings are preferred.

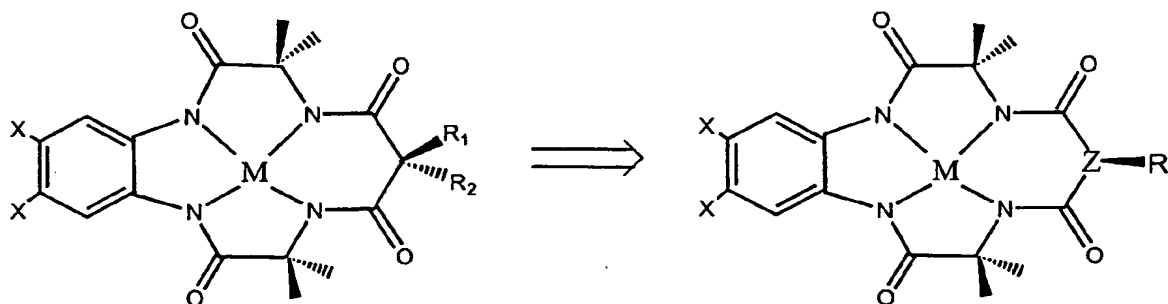
5 If cyclic groups are formed, or if there are residual R groups remaining from combination at adjacent sites, the residual R groups and the substituents on the cyclic groups are chosen in the same manner as for normal single node or multi node substitution (including the possibility of further R group fusions to yield additional spiro, benzo, substituted benzo, heterocyclic, substituted heterocyclic, cycloalkyl, substituted cycloalkyl, cycloalkenyl or
10 substituted cycloalkenyl ring structures).

 An important point is that the definitions for both single node and multi node substitution can function *recursively*, e.g. substituted o-phenylene diamine => substituted heterocyclic o-phenylene diamine => substituted spiro-cycloalkyl heterocyclic o-phenylene
15 diamine etc.



Schematic 3: Replacement at three variable positions can either be by three $-C(R_a)(R_b)-$ units or two of the variable positions can be combined to make up part of an aryl or heterocyclic ring structure with the third position being replaced by a $-C(R_a)(R_b)-$ unit or the three variable positions can all be combined to form part of a fused diaryl, fused aryl heterocyclic, or fused diheterocyclic ring structure.

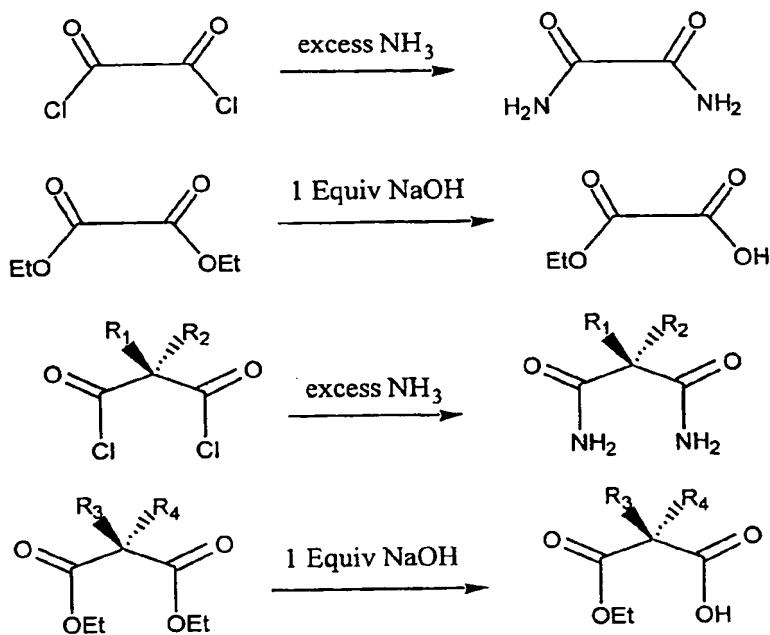
Additional potential oxidatively robust macrocyclic ligands are based on replacing the cyclic carbon of the six-membered ring of the metallated macrocycles described above with a heteroatom Z selected from Group 15 of the Periodic Table, preferably N, P or As, shown below.



The metal containing macrocyclic ligand with a carbon at the central position of the six membered ring is shown on the left. A metal containing macrocyclic ligand with a Group 15 heteroatom, Z, at the central position of the six membered ring is shown at the right.

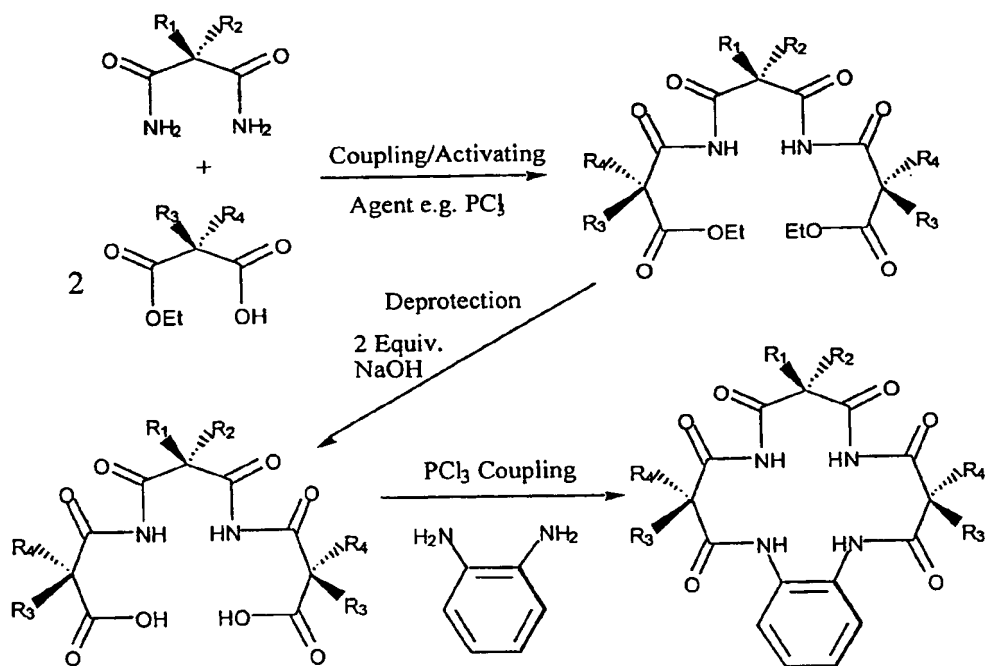
- 5 Starting from the basic tetradentate macrocycles, the macrocycles in Table 3 contain additional N or O substituents. Some representative synthetic approaches and starting materials are shown below. Synthesis of many of the imide containing macrocycles is a straightforward extension of the existing amide containing macrocyclic syntheses. Malonic and oxalic acid derivatives are first converted to terminal amides, then the terminal amides
- 10 are reacted with an activated molecule to form an imide containing macrocyclic linker. Once the macrocyclic linker is obtained it is coupled with a diamine to form an imide containing macrocycle. This approach can generate a wide variety of imide containing macrocycles.

Malonic and Oxalic acid derivatives useful in the synthesis of imide containing macrocycles are shown below, Sequence 4.



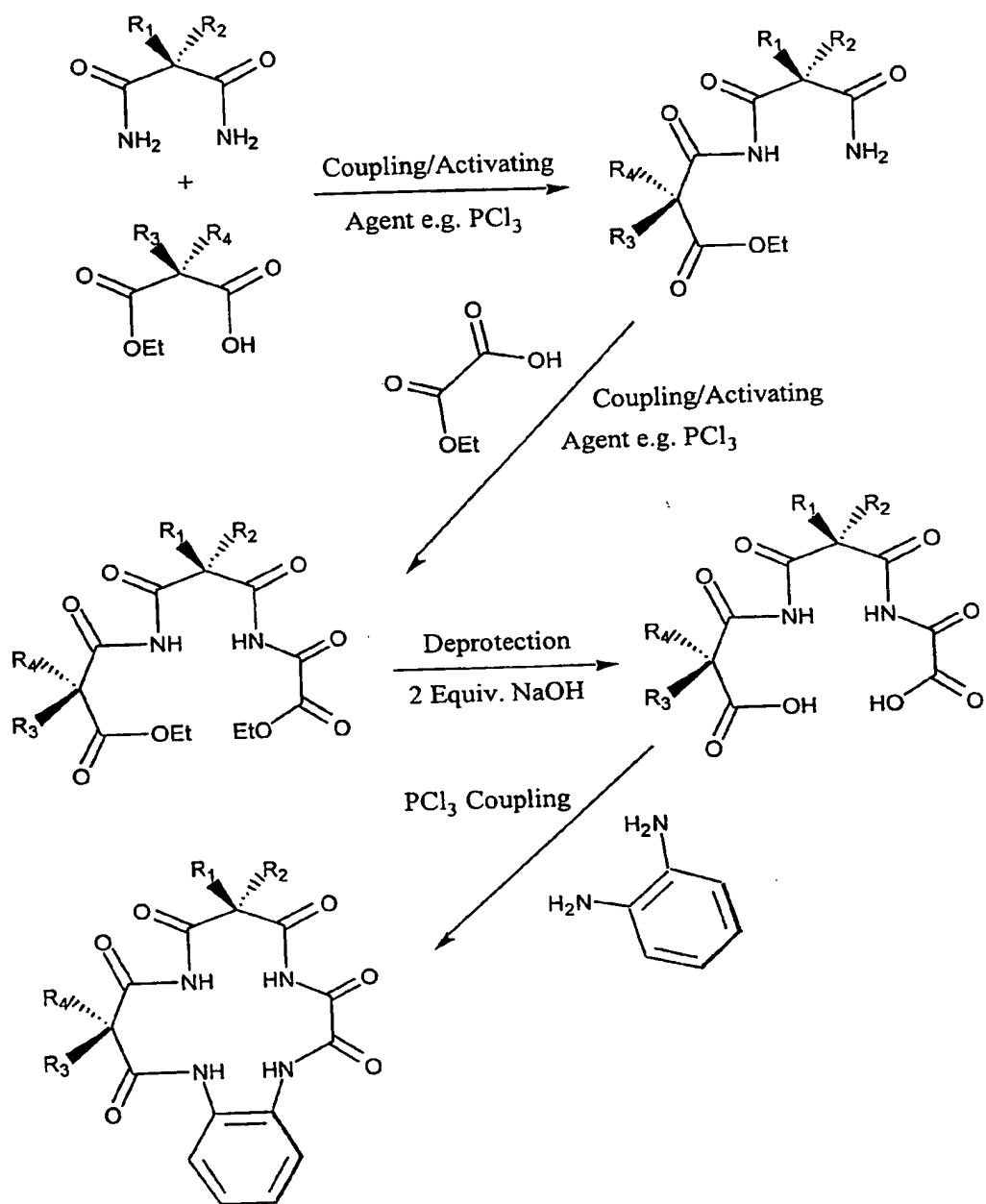
Sequence 4

The synthesis of an imide containing macrocycle by an extension of the synthetic methodology shown in Sequence 3 is shown below in Sequence 5.



Sequence 5

5 The same approach can also yield asymmetrically substituted imide containing macrocycles as shown in the next sequence. Starting materials for N-substituted macrocycles are not as abundant commercially as for the corresponding O-substituted macrocycles. However, this problem can be overcome by taking advantage of the reactivity of the N group to synthesize the required starting materials. Standard synthetic techniques well known to those skilled in the art will yield a variety of N-substituted starting materials. For example, starting from a desired NR group, e.g. methylamine, aniline, N-trifluoro amine then N-alkylation or N-acylation can be employed to generate useful N-substituted synthetic intermediates as shown below in Sequence 6.

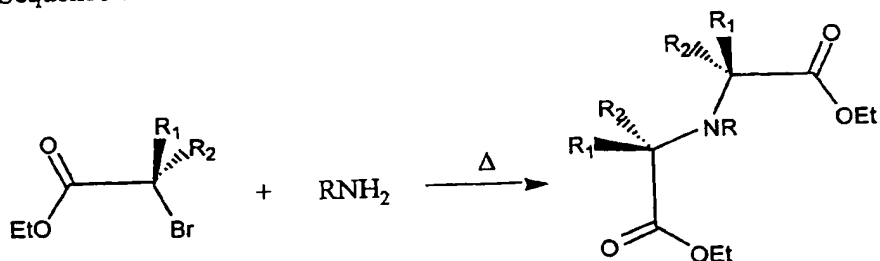


Sequence 6

5 Synthesis of asymmetrically substituted imide containing macrocycles by an extension of the existing macrocyclic synthetic pathways.

N-Alkylation

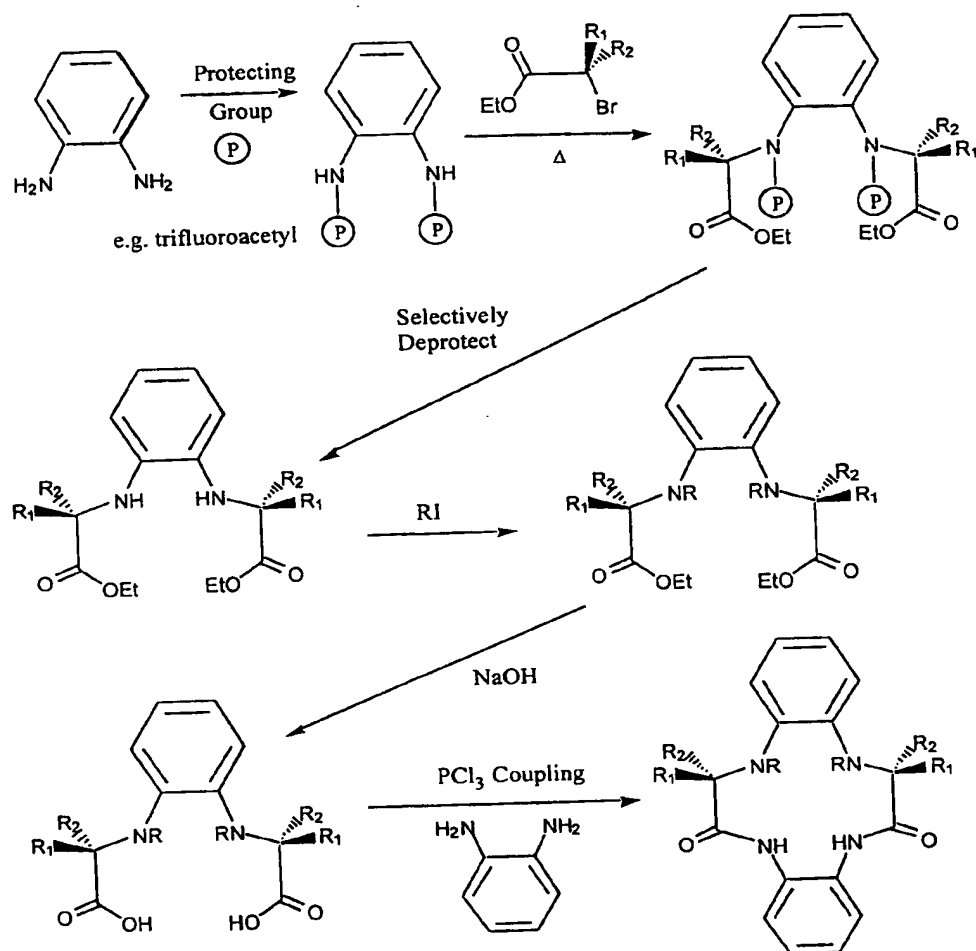
N-alkylation can generate useful portions of the macrocyclic framework as shown below, Sequence 7.



Sequence 7

5

N-alkylation can also be used to generate NR containing analogs of the existing macrocyclic linkers which can then be further coupled via amide forming reactions to form complete NR containing macrocycles by the following sequence, Sequence 8.



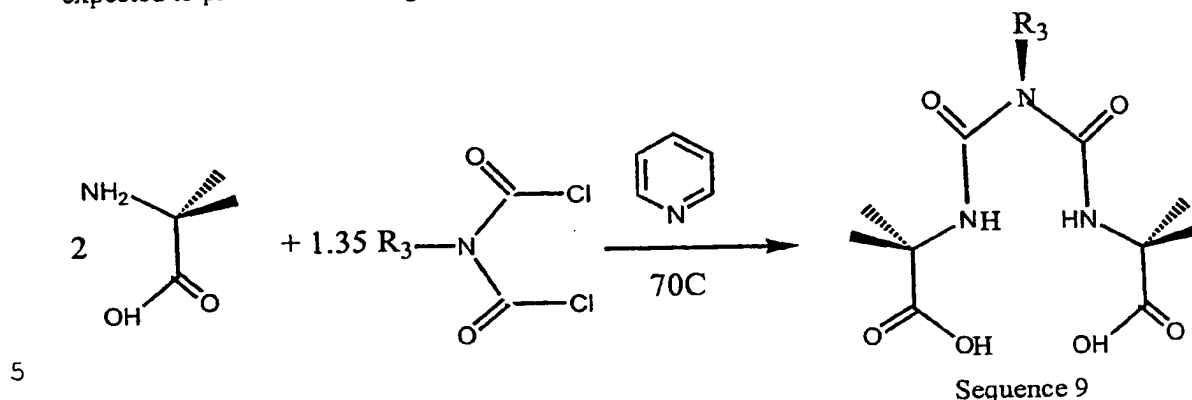
8.

Sequence 8

Sequence 7: N-alkylation can be used to generate NR containing analogs of the macro-linker which can then be macrocyclised according to existing methodology.

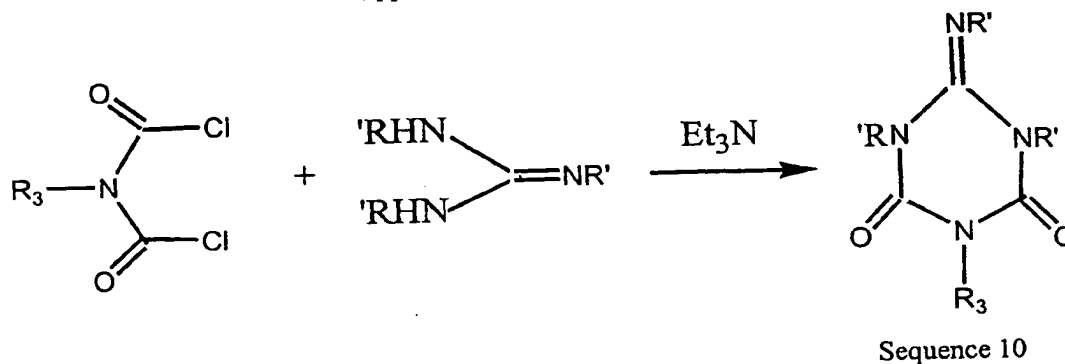
N-Acylation

Acylation of the amino acid with the bis-(chlorocarbonyl)-amine, Sequence 9, is expected to proceed in a straightforward manner.



10

Acylation of an *N*-substituted bis-(chlorocarbonyl)-amine with the amino acid used in Sequence 3. Pyridine is used as the catalyst in the acylation reaction. An analogous reaction between the bis-(chlorocarbonyl)-amine has been reported by R. Richter et al., *Tetrahedron Letters*, pp.1875-1878 (1974), Sequence 10.



15

The synthetic methodology uses components that are similar to those reagents described as useful starting materials for the synthesis of the metallated macrocycles described above. The reagent to be replaced in this example is the diacylchloride in Sequence 3 above.

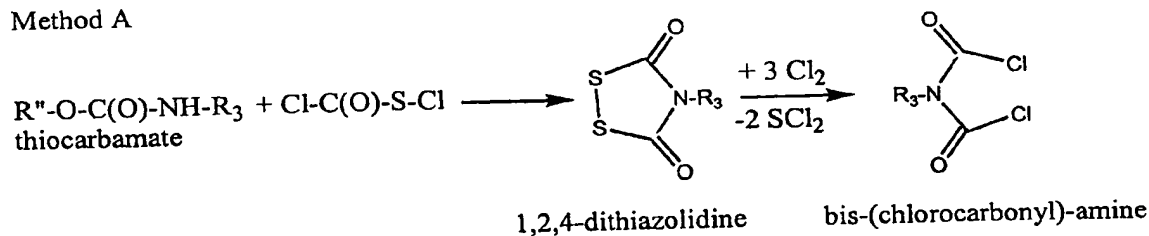
The "diacylchloride" analog necessary for the synthesis is shown in Sequence 9. There are two synthetic routes Method A, (See, Slomczynska, U. et al., *J. Heterocyclic Chem.* Vol. 21, pp. 241-246 (1984); Zumach et al., British Patent No. 1,136,737) and Method B

(See, Zumach, G., British Patent No. 1,136,950) described in the literature that will lead to the desired compound. It has been stated that Method A leads to a purer form of the intermediate designated as the "1,2,4-dithiazolidine." The 1,2,4-dithiazolidine with $R = C_6H_5$ has been successfully prepared by Method B. Method B was chosen initially because it is simpler than Method A as Method A requires the additional step of synthesizing the desired thiocarbamate, and if the impurities do not inhibit macrocycle formation this will be the preferred synthetic route. Conversion of the 1,2,4-dithiazolidine to the bis-(chlorocarbonyl)-amine, Sequence 9, also is described in the literature. See, Zumach, G. et al. *Synthesis* pp. 542-543 (1970).

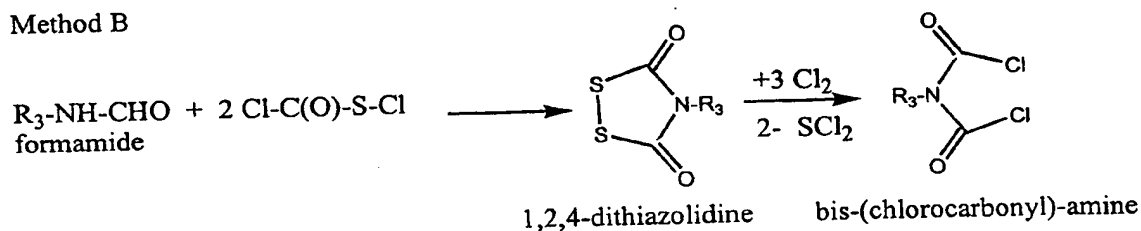
Two viable routes to N-substituted bis-(chlorocarbonyl)-amines are shown below,

Sequence 11.

Method A



Method B



Sequence 11

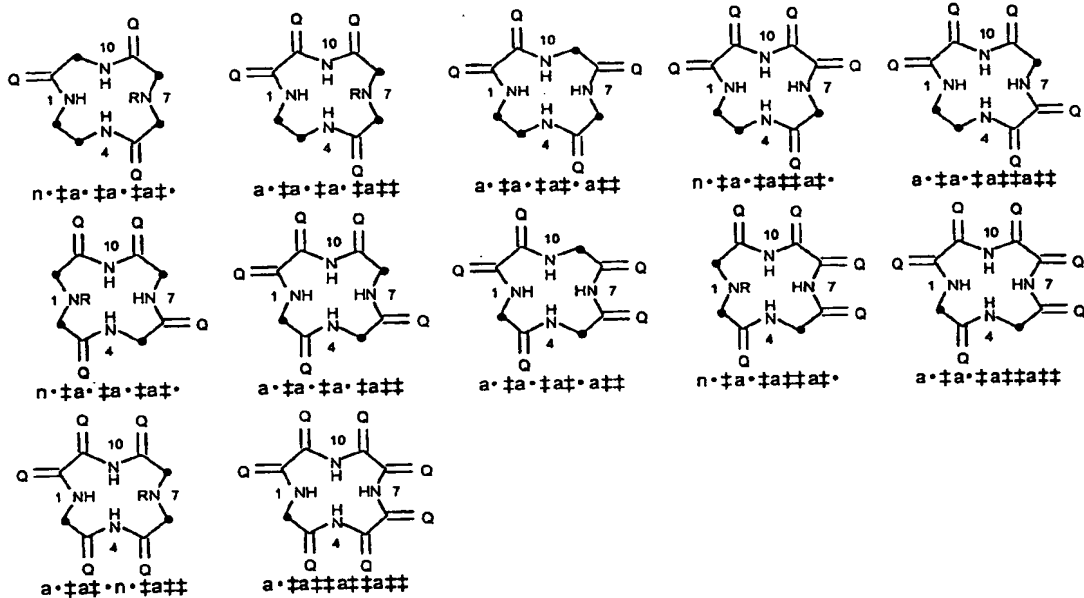
The possible variations in macrocyclic structure for Compound 1 with N and O substitution in the ligand framework are shown in Table 4 below.

Table 3

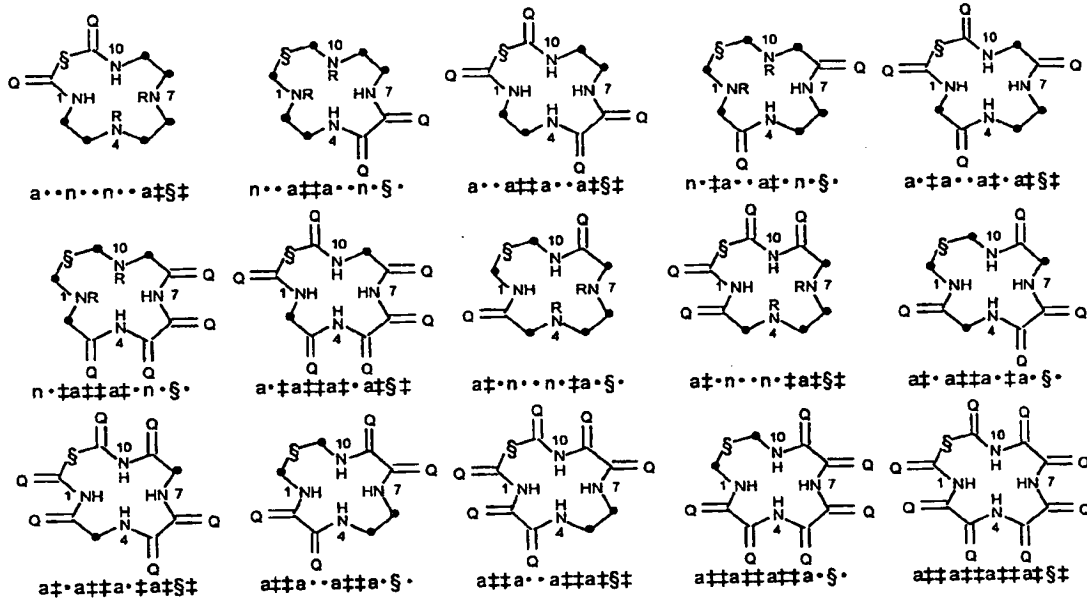
5555 Macrocycles



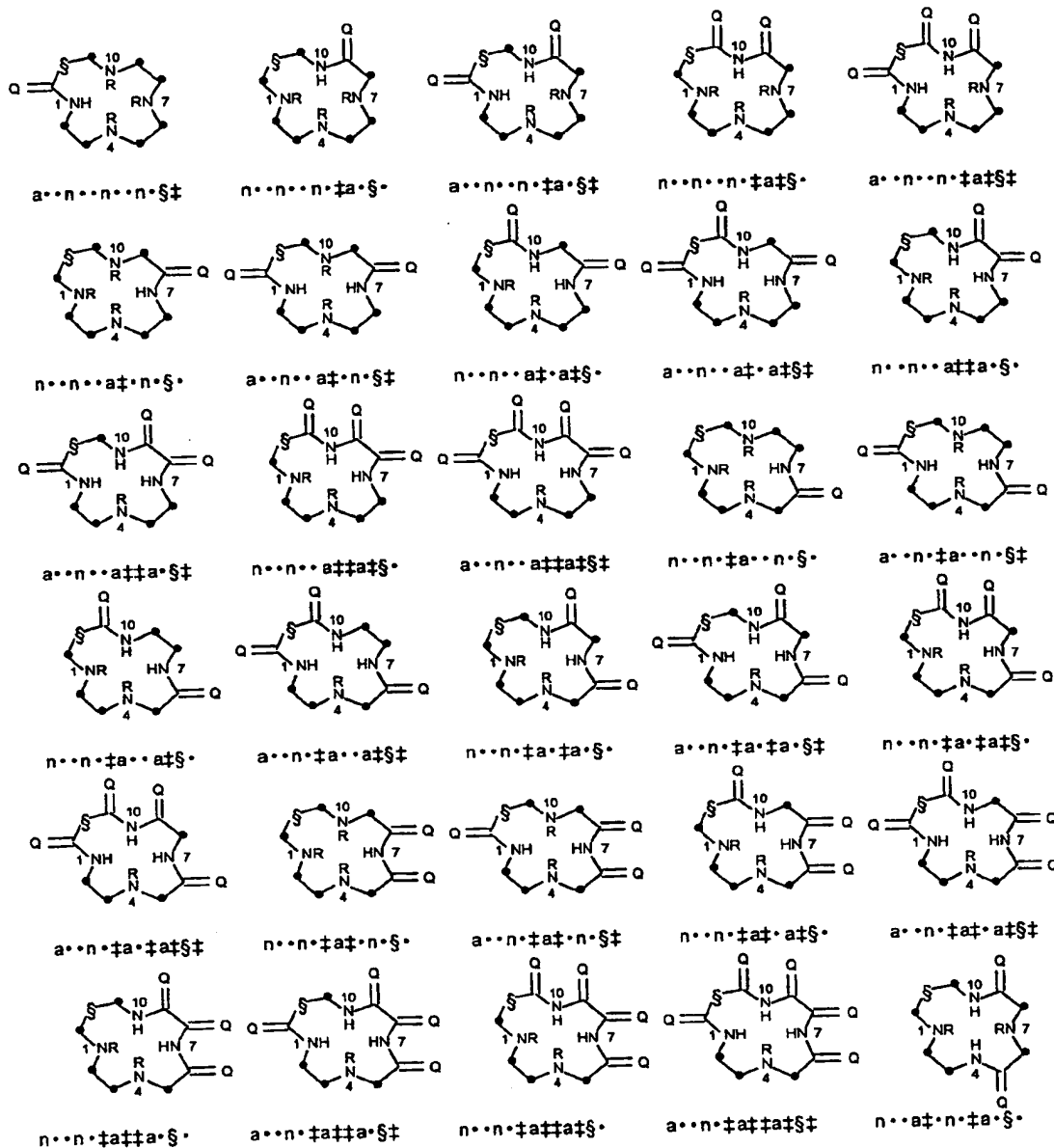
5555 Macrocycles (cont.)



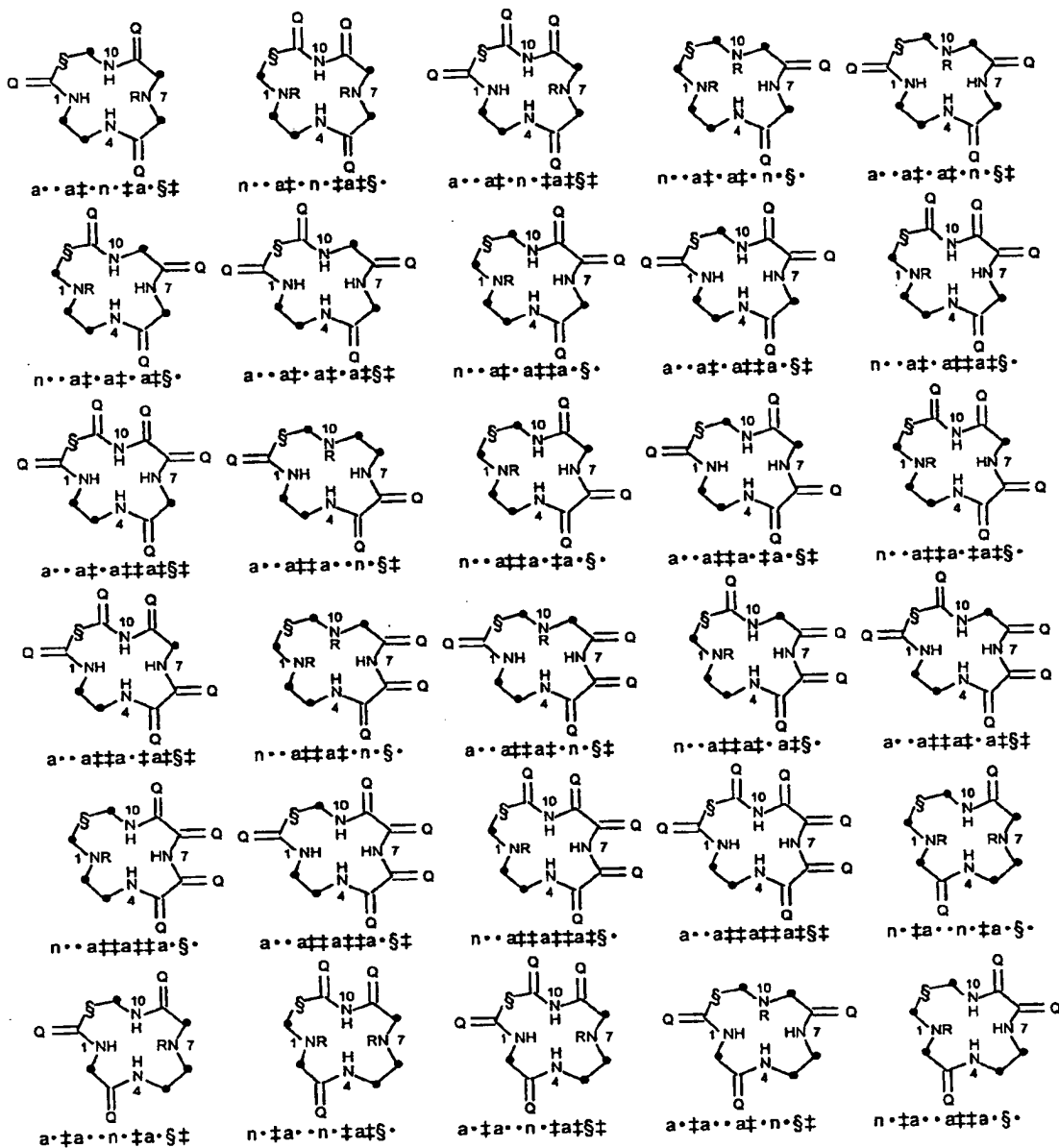
5556 Macrocycles



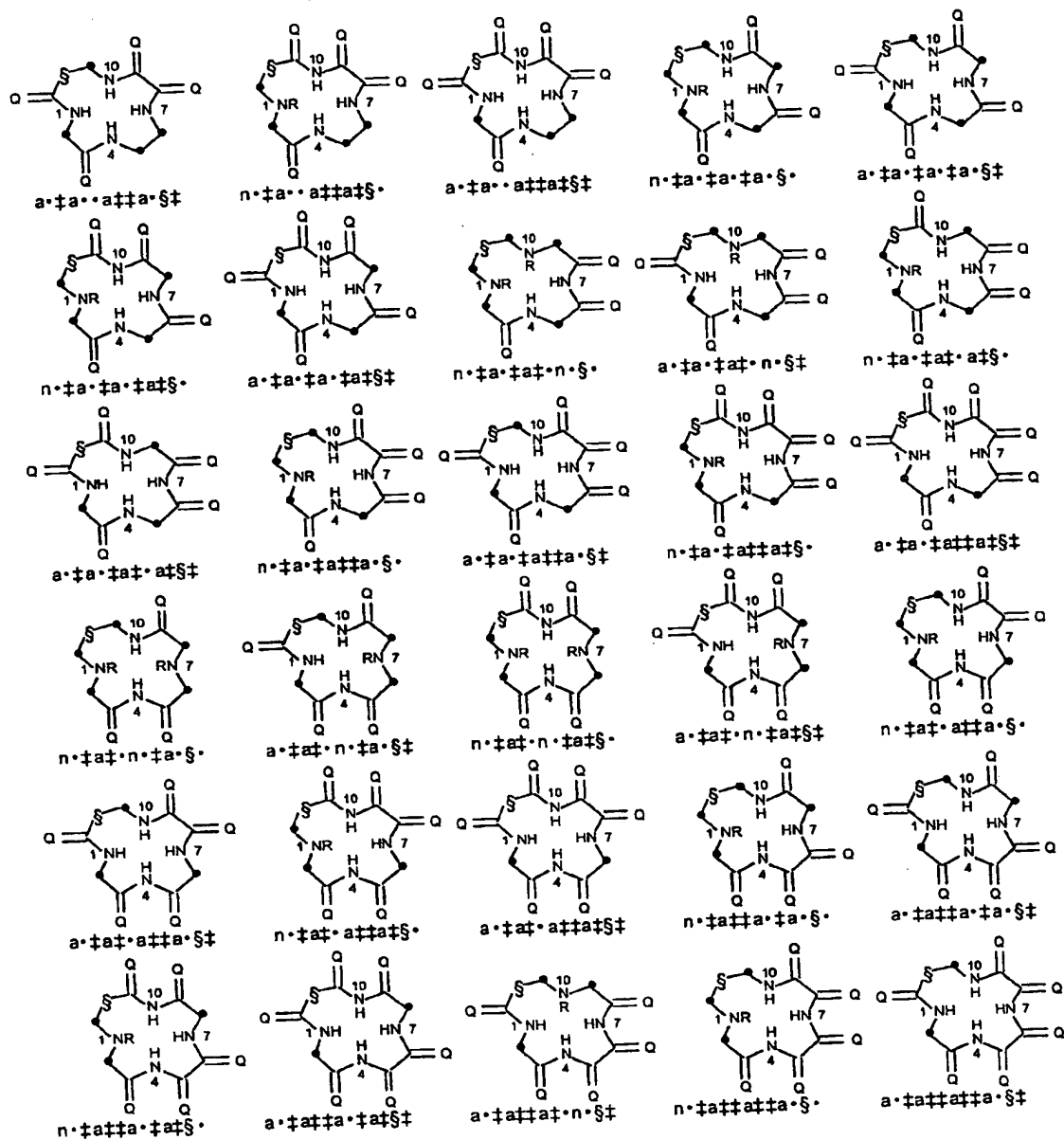
5556 Macrocycles (cont.)



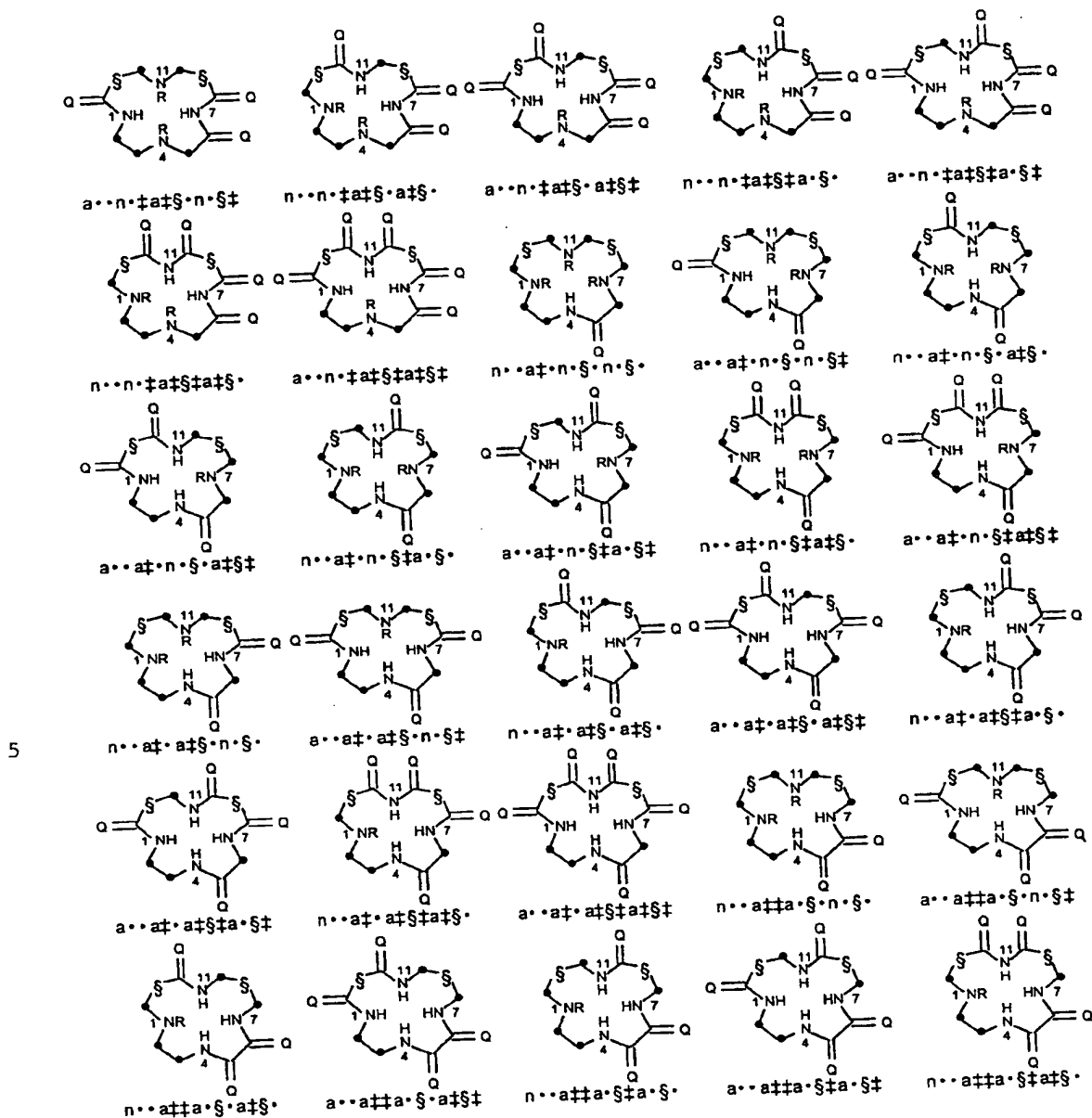
5556 Macrocycles (cont.)



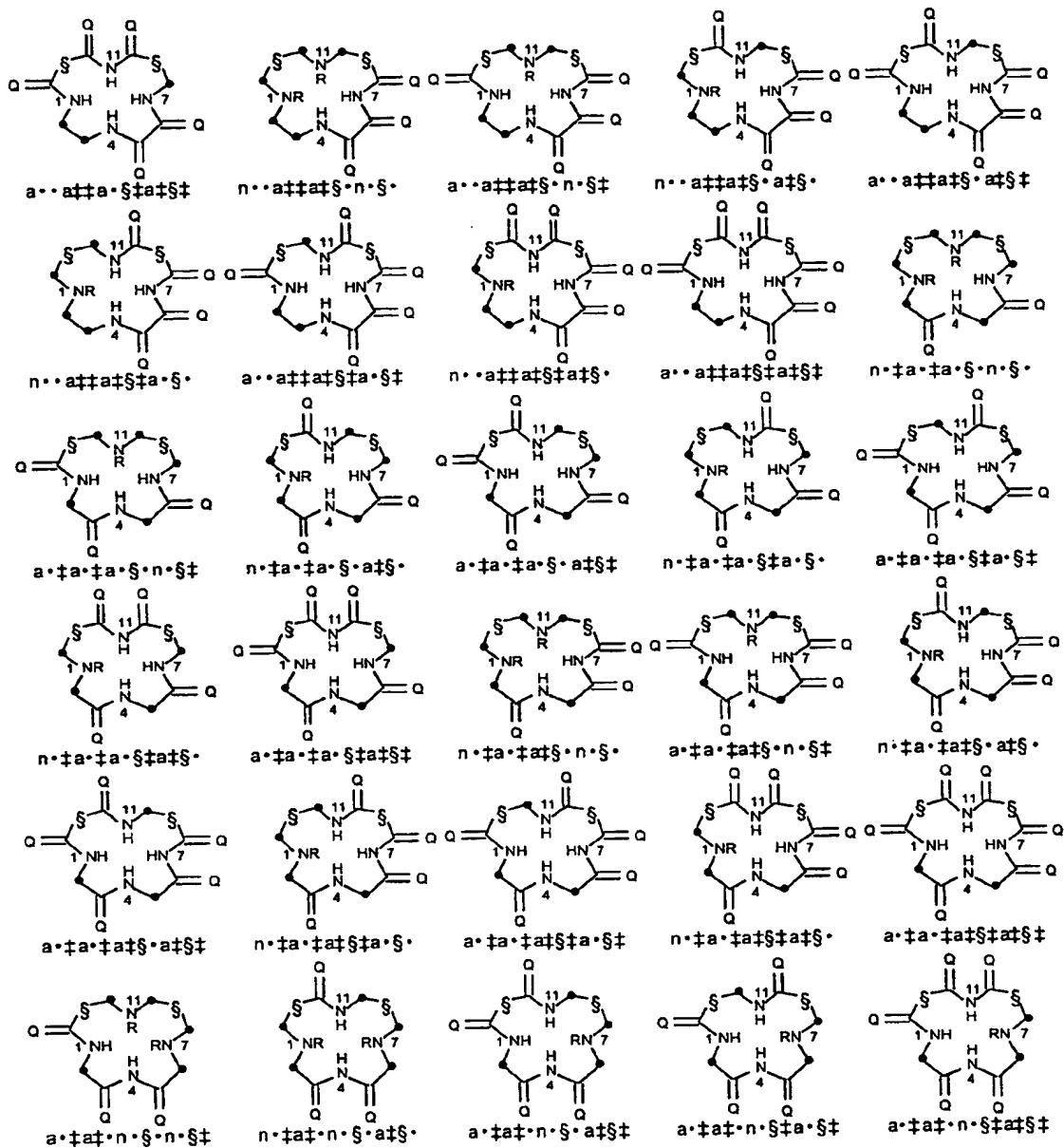
5556 Macrocycles (cont.)



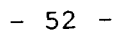
5566 Macrocycles (cont.)



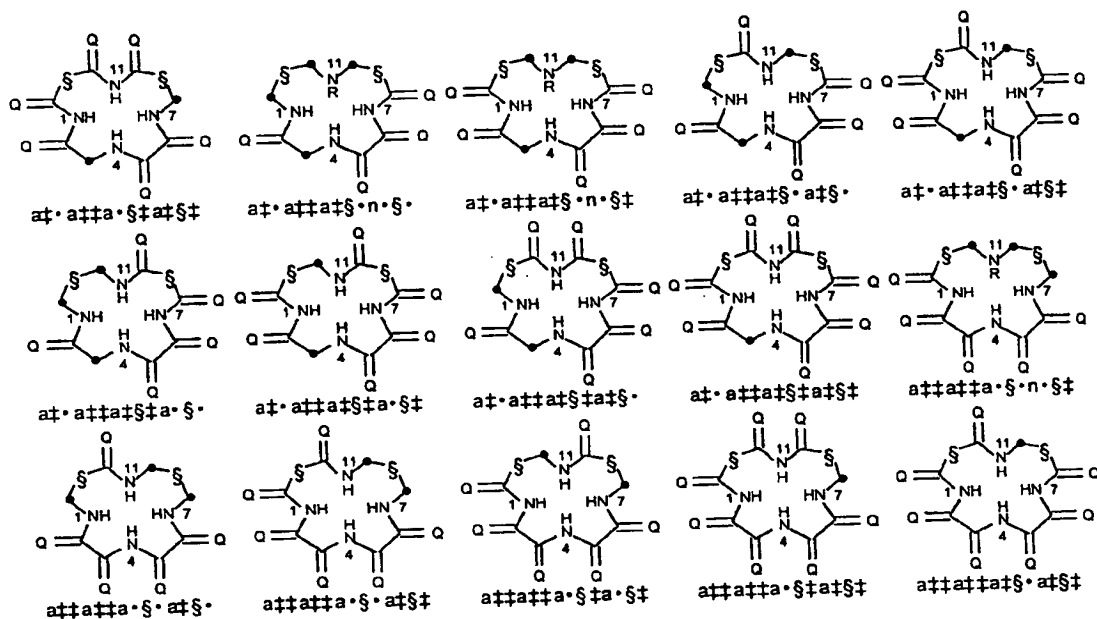
5566 Macrocycles (cont.)



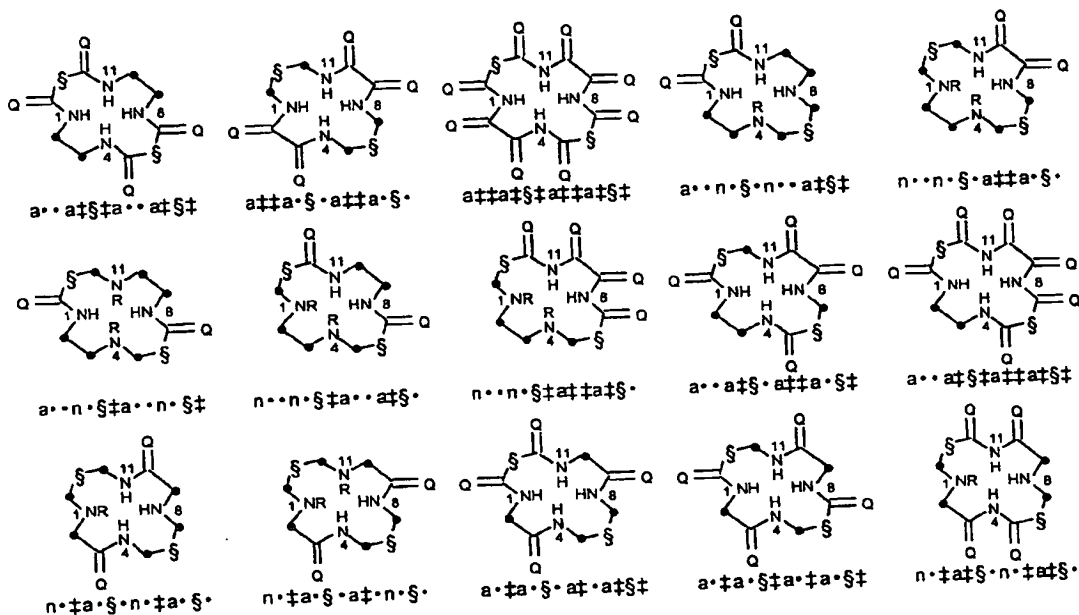
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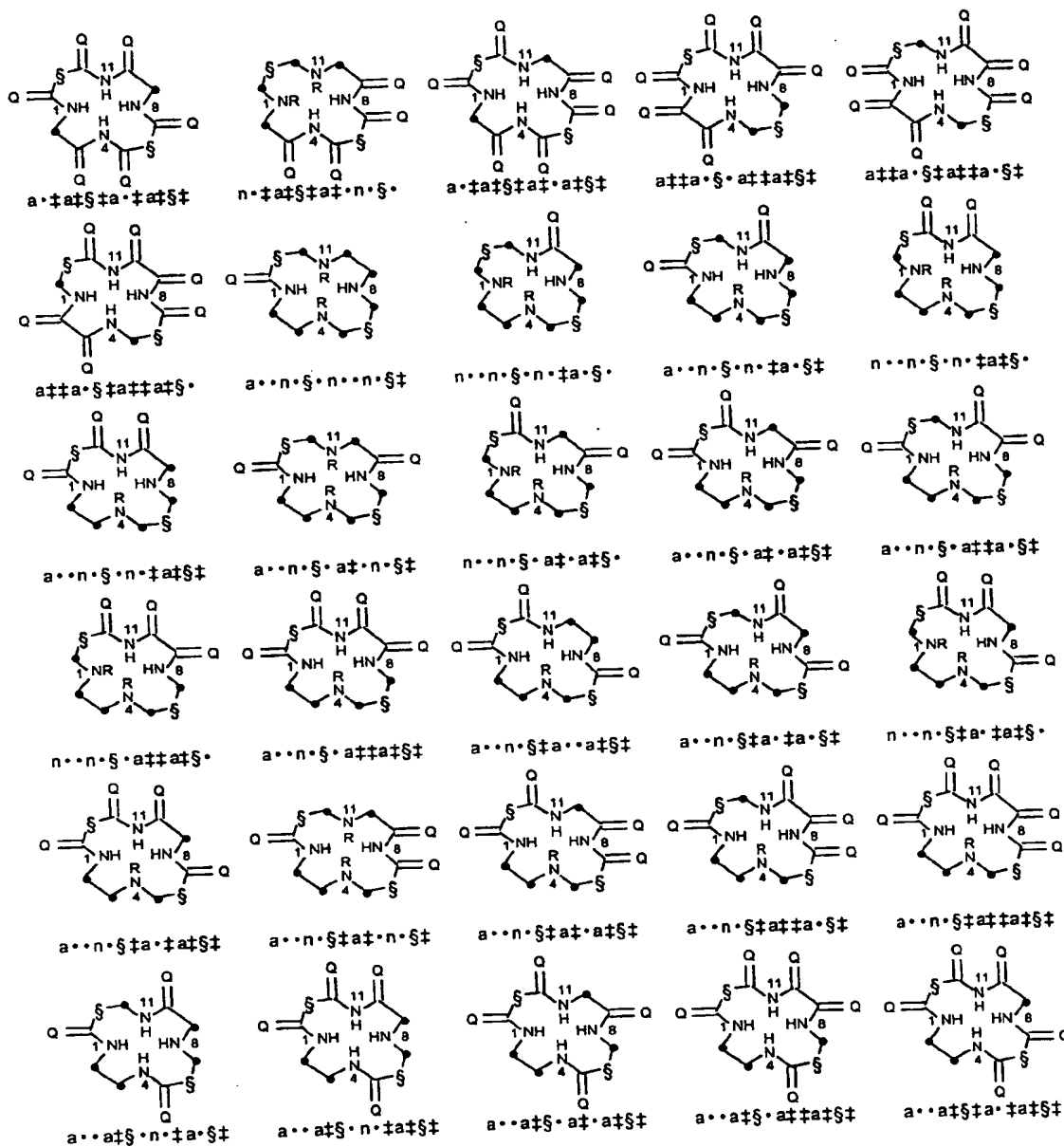
5566 Macrocycles (cont.)



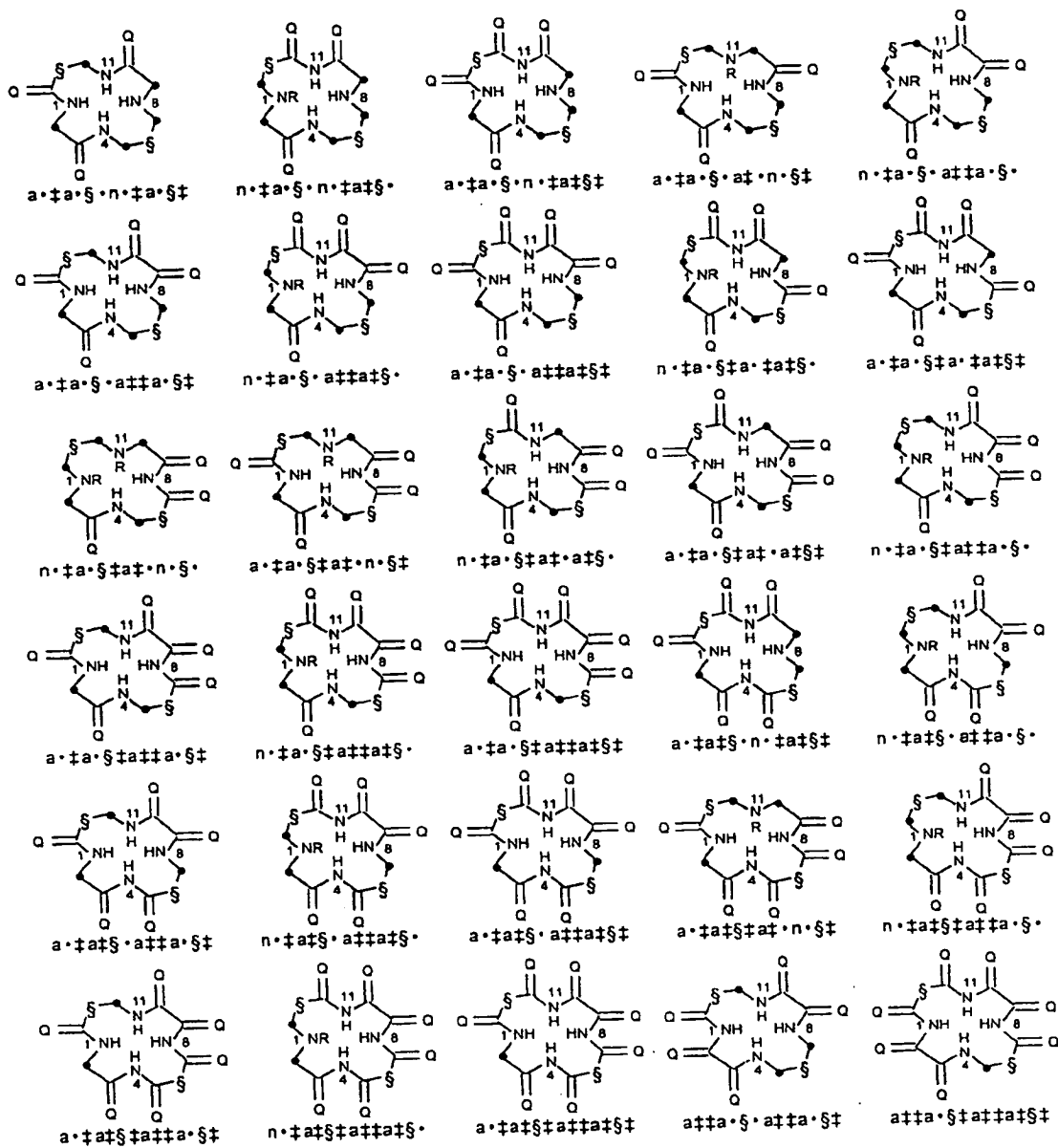
5656 Macrocycles



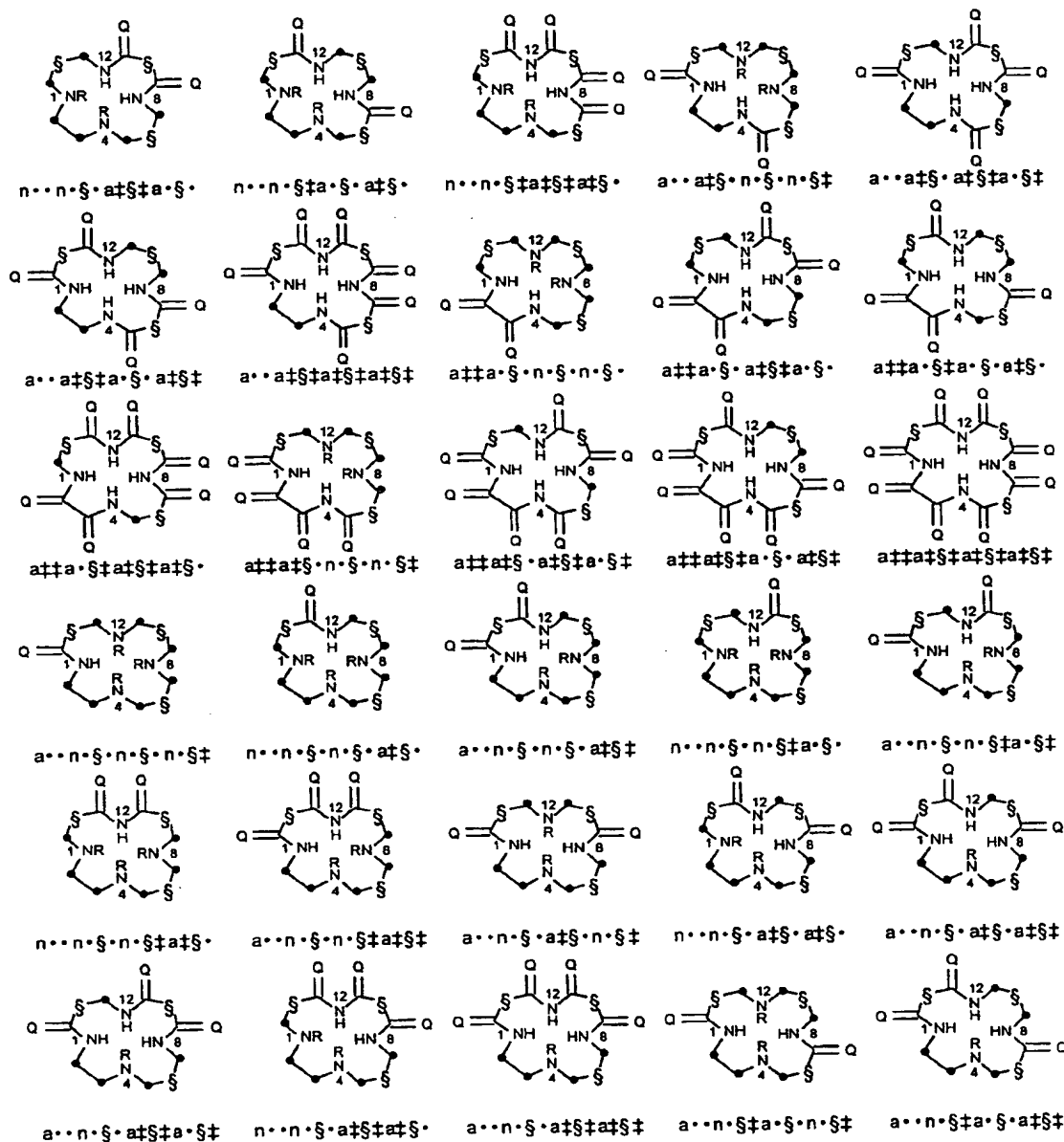
5656 Macrocycles (cont.)



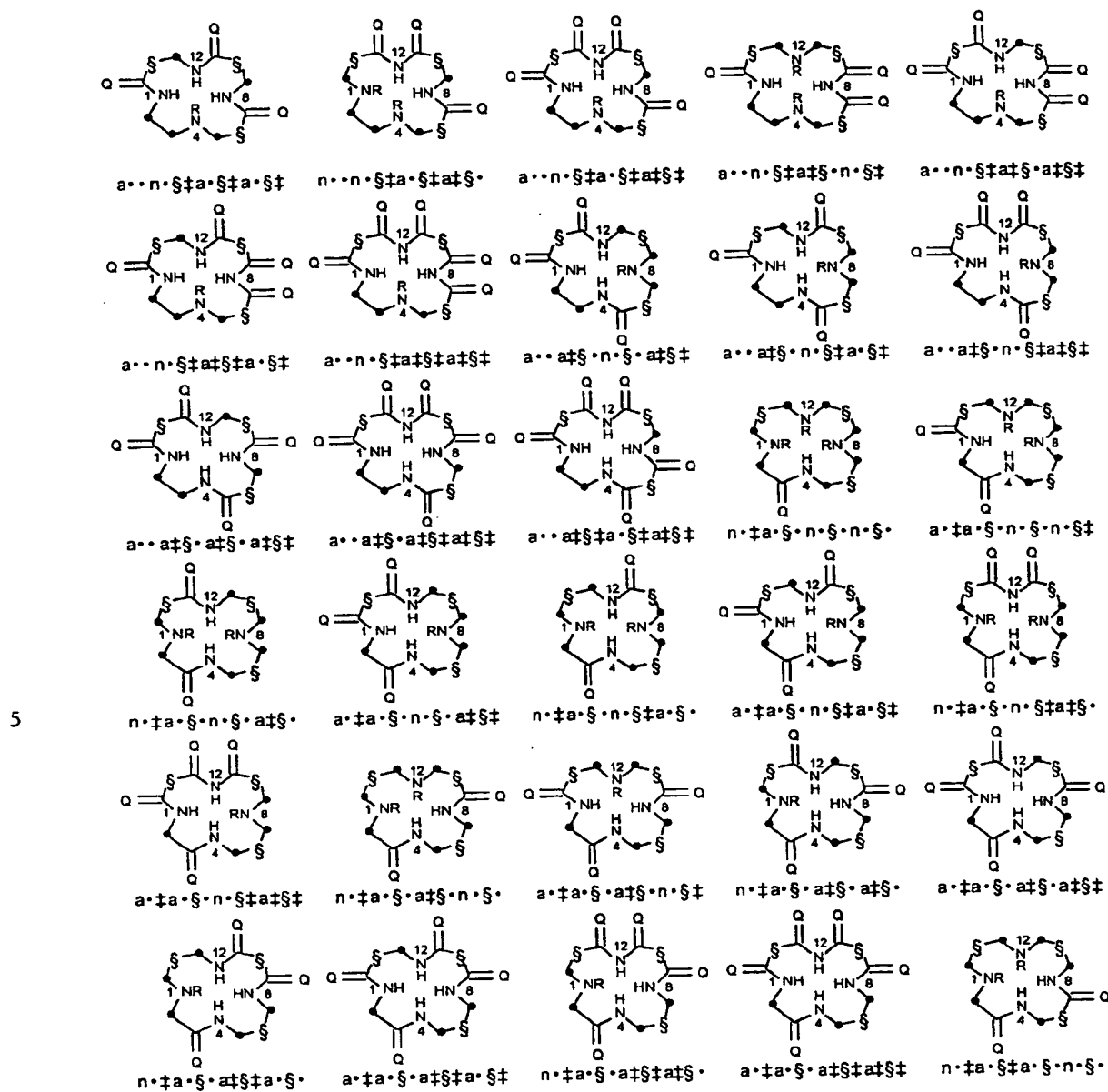
5656 Macrocycles (cont.)



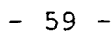
5666 Macrocycles



5666 Macrocycles (cont.)

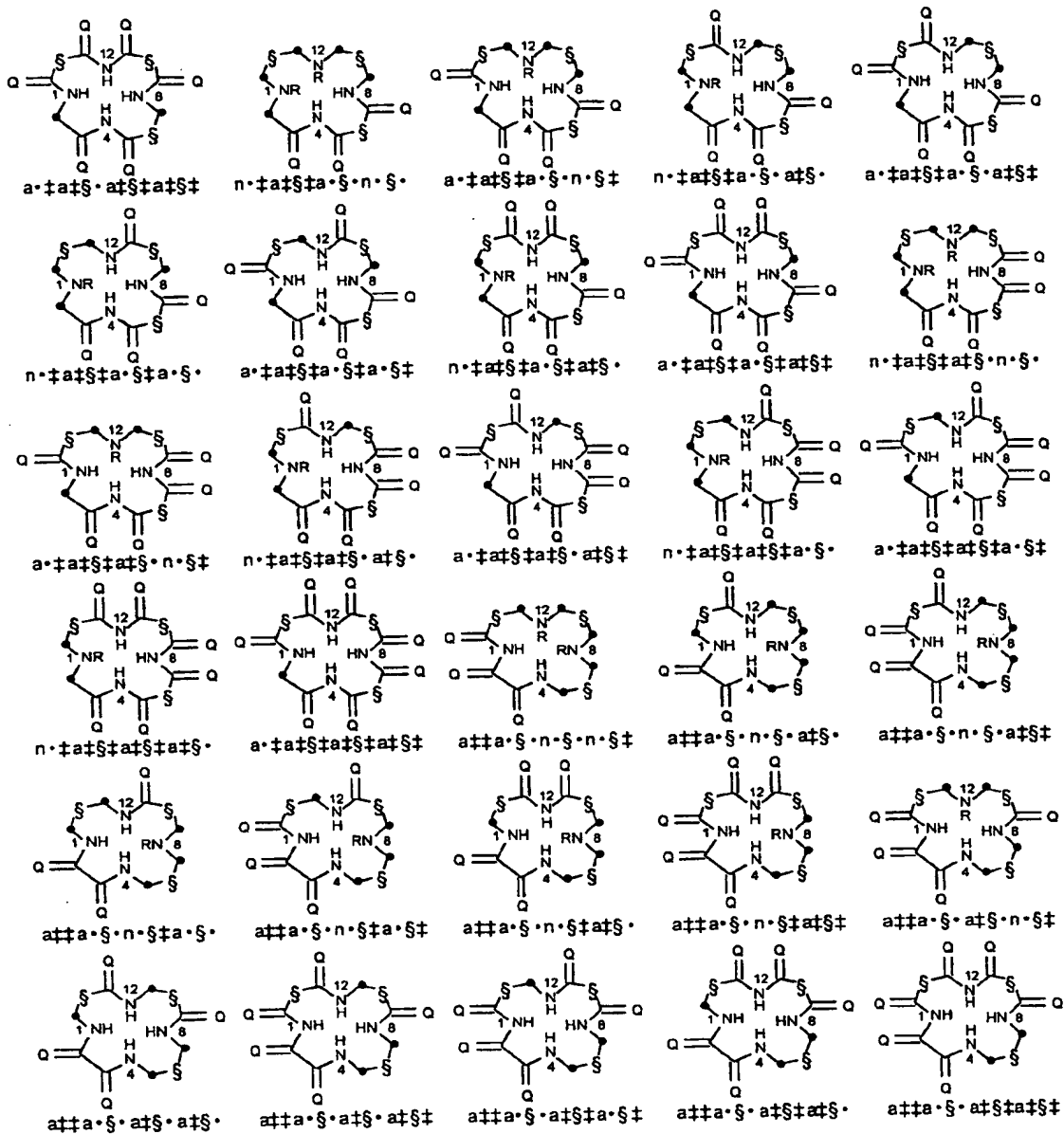


5

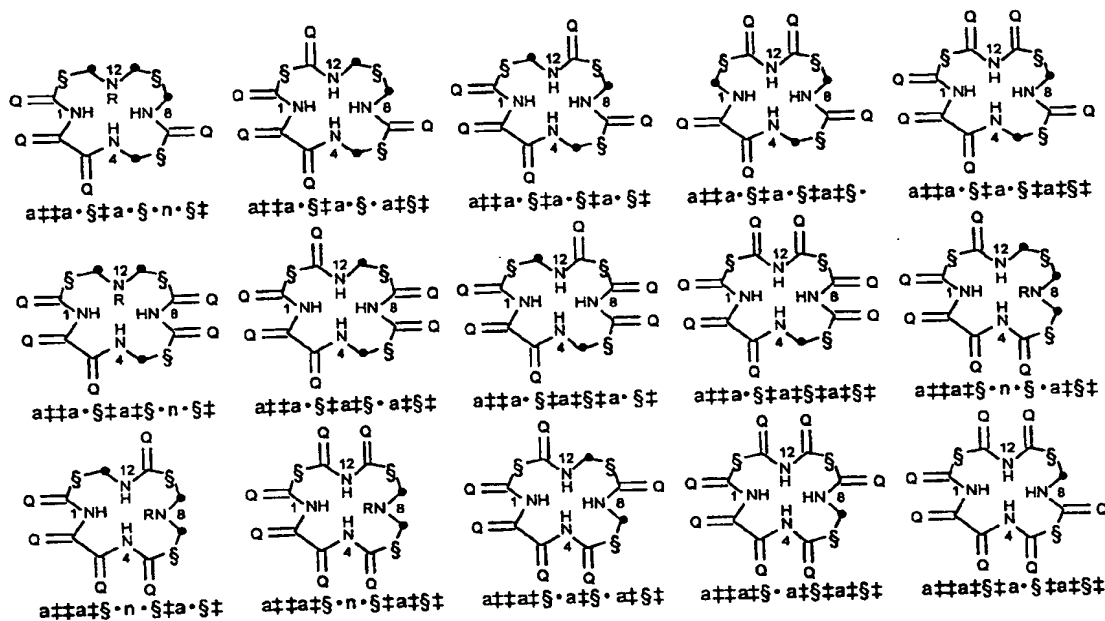


5666 Macrocycles (cont.)

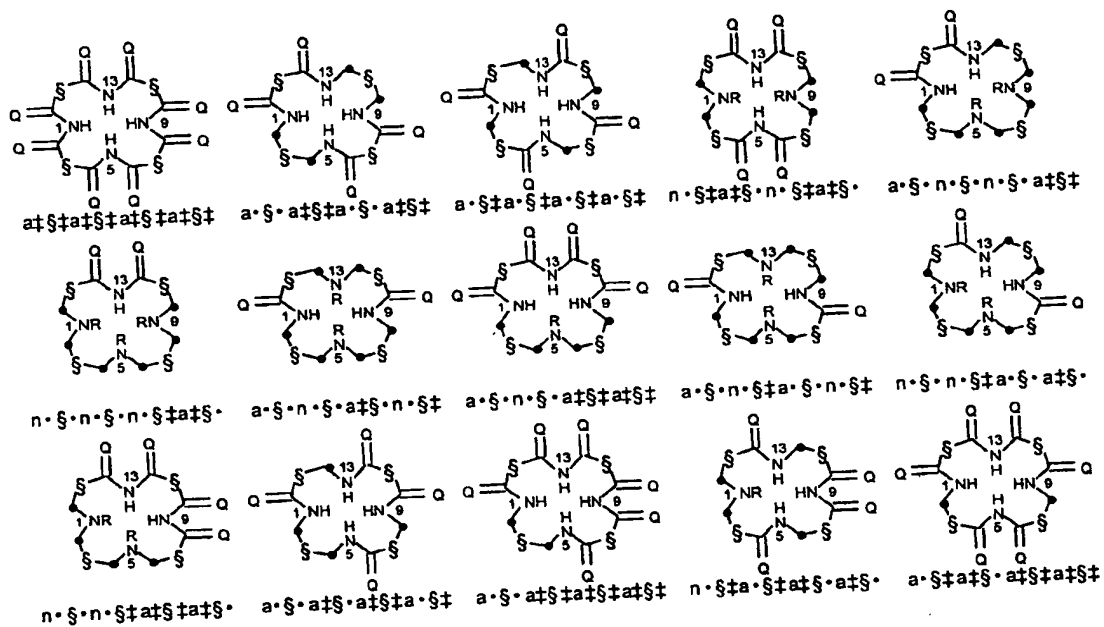
5



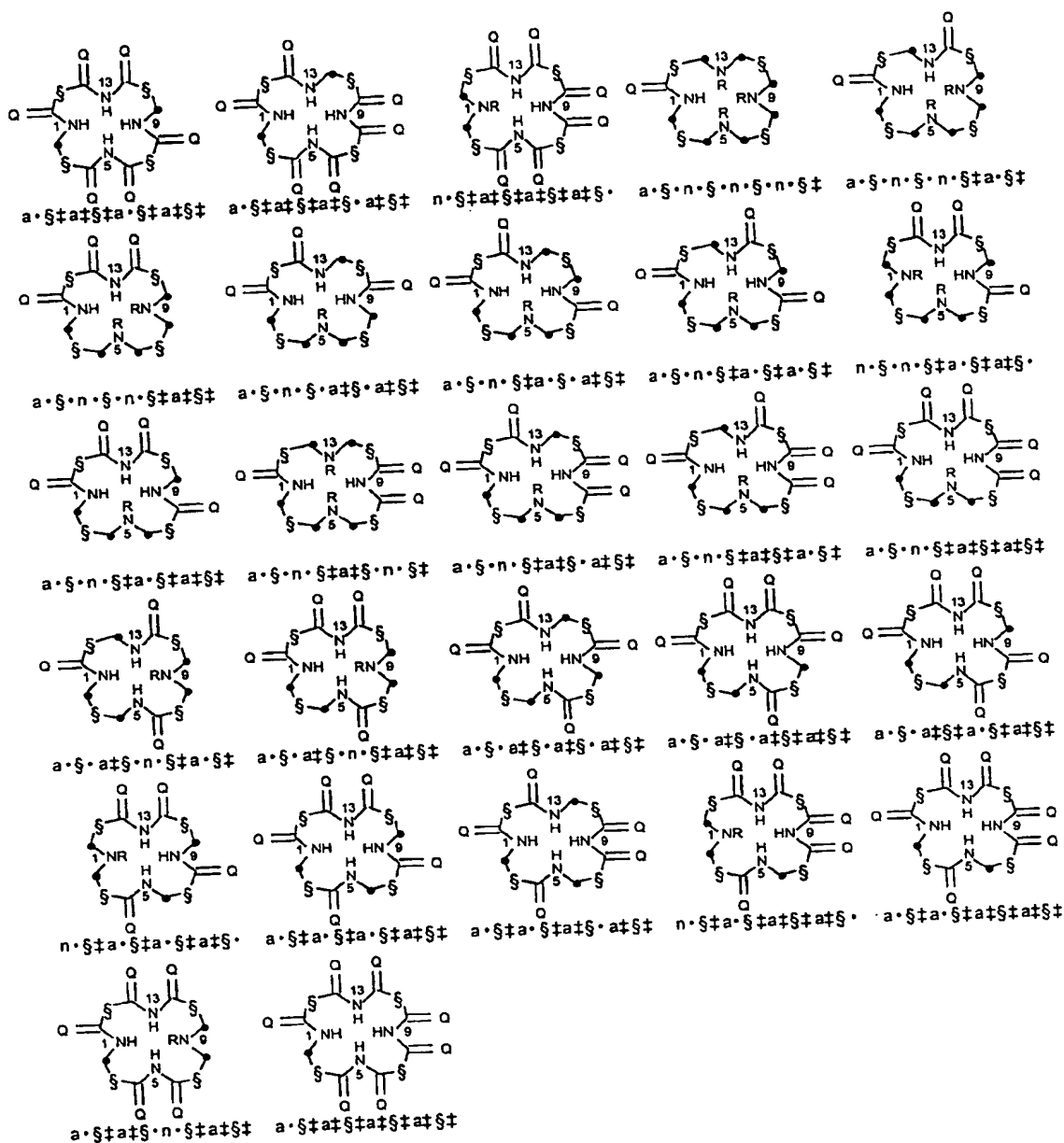
5666 Macrocycles (cont.)



6666 Macrocycles



6666 Macrocycles (cont.)



Explanation of Symbols for Table 3:

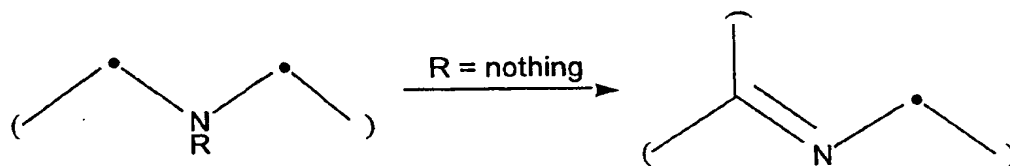
The macrocyclic ligands shown in Table 3 are grouped into 6 families based on the sizes of the chelate rings formed upon metal coordination. For instance, a 5555 macrocycle consists of four five-membered metal containing chelate rings. Below each picture is the textual description of the substituents that form the particular macrocycle. The symbols start at the first position, indicated in the structures of Table 3 by a 1, and then progress around the ring in an anti-clockwise direction; it is implicit in the notation that the last position of the text string is connected to the first position in order to form the macrocycle. The meanings of the symbols are as follows:

- 10 "•" represents a carbon containing node able to be substituted as described previously with a pair of R_1 , R_2 , R_3 , R_4 , R_5 and R_6 .

"a" represents an NH group

- "n" represents a DX group, wherein each D is a donor atom, such as N or O, and each X is a position for addition of a substituent and each position is (i) not occupied such that a double bond is formed between D and an atom adjacent to D, or (ii) is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, phenoxy, halogen, halogenated alkyl, halogenated aryl, halogenated alkenyl, halogenated alkynyl, perhaloalkyl, perhaloaryl, a substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted cycloalkenyl ring, a substituted or unsubstituted saturated heterocyclic ring, a substituted or unsubstituted unsaturated heterocyclic ring, and at least one X is hydrogen, and when D is O, the position is not occupied;

- 20 The X group may also form connections to other nearby substitutable (• or X) positions of the molecule to allow the formation of 4, 5 and 6 membered heterocyclic ring systems. X may be nothing as a special case, as shown below, which allows additional multiple bonding to take place between the D group and an adjacent carbon atom, but preserves the presence, for example, of the nitrogen lone pair as a donor to the metal ion.



25 "‡" represents a C=Q unit, where the Q groups can be the same or different and is chosen

from O or ZR'.

"§" represents a special substitutable position, where the § group is chosen from •, ZR', C=Q, or ZH. Z is selected from the group consisting of N, P, or As and R' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, phenoxy, halogen, halogenated alkyl, halogenated aryl, halogenated alkenyl, halogenated alkynyl, perhaloalkyl, perhaloaryl, a substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted cycloalkenyl ring, a substituted or unsubstituted saturated heterocyclic ring, a substituted or unsubstituted unsaturated heterocyclic ring, and at least one X is hydrogen,

10

Some representative examples of commercially available and/or synthetically versatile Linker, Arm and Bridge starting materials are shown in Tables 4, 5 and 6, respectively. A macrocyclic amide containing compound having the desired chelate ring configuration shown in Table 3, i.e., 5555, 5556, 5566, 5656, 5666 or 6666, and variations thereof, can be constructed by reference to the general choice and combination of starting materials for various chelate configurations shown in Table 2, i.e., parent, protected/activated or hidden, followed by the choice of the specific starting materials from Tables 4, 5 and 6 or the materials synthesized by Sequences 4-11. Use of those functionally and similar starting materials in the new synthetic method will provide a macrocyclic amide containing compound having a chelate ring configuration and substituent array suited to a particular end use. The symbol * in the Tables indicates a substituent that is comparatively robust towards oxidation. The symbol *** ‡ in the Tables indicates substituents that are very oxidatively robust. Table 4 identifies some representative dicarboxylic acid malonate derivatives, i.e. Linkers, of interest for the preparation of macrocyclic amide containing compounds, either † in parent, hidden, or protected/activated forms.

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Table 4 - The MalonatesDerivatives of Oxalic Acid (5cc)

Registry #	Compound Name
	*Oxalyl Chloride

5 Derivatives of Malonic Acid (6cc)

Registry #	Compound Name	Registry #	Compound Name
------------	---------------	------------	---------------

Disubstituted malonates

	31696-00-1	*Diethyl butylethyl-malonnate		*Diethyl di-n-octyl-malonnate
10	00596-76-9	*Diethyl butylhexyl-malonnate	24251-93-2	*Diethyl di-n-pentyl-malonnate
	00083-27-2	*Diethyl butylmethyl-malonnate		*Diethyl di-2-propenyl-malonnate
15		*Diethyl butylethyl-malonnate	03195-24-2	*Diethyl di-n-propyl-malonnate
		*Diethyl butylpentyl-malonnate		*Diethyl ethylheptyl-malonnate
		*Diethyl butylpropyl-malonnate		*Diethyl ethylhexyl-malonnate
20		*"2,2-Diethyl-butyrir acid"	00133-13-1	*Diethyl ethyl (1-methyl butyl) malonnate
	18719-43-2	*Diethyl "1,1-cyclo-butane dicarboxylate"		*Diethyl ethylmethyl-malonnate
	53608-93-8	*Diethyl "1,1-cyclo-propane dicarboxylate"	02049-70-9	*Diethyl ethyl (1-methyl-propyl) malonnate
25	01559-02-0	*Diethyl decylethyl-malonnate		*Diethyl ethylnonyl-malonnate

	05077-96-3	*Diethyl decylmethyl-malonate	05408-35-5	*Diethyl ethyloctyl-malonate
		*Diethyl diallyl-malonate	00076-67-5	*Diethyl ethylpentyl-malonate
5	00597-55-7	*Diethyl di-n-butyl-malonate		*Diethyl ethylphenyl-malonate
	00596-75-8	*Diethyl di-n-decyl-malonate	71691-56-0	*Diethyl ethylpropyl-malonate
10		*Diethyl diethyl-malonate		*Diethylmethyl(2-methylbutyl) malonate
		*Diethyl di-n-heptyl-malonate		*Diethyl methyl(2-methylpropyl) malonate
		*Diethyl di-n-hexyl-malonate	34009-61-5	*Diethyl methylnonyl-malonate
15		*Diethyl dimethyl-malonate	01575-67-3	*Diethyl methylphenyl-malonate
	01619-62-1	*Diethyl di-n-nonyl-malonate	58447-69-1	*Diethyl methylpropyl-malonate
20		*"1,1-cyclopropane dicarboxylate"	00083-27-2	*Diethyl methyl-iso-propylmalonate
		*"1,1-cyclopentane dicarboxylate"		*"1,1-cyclobutane dicarboxylate"
		*ditrifluoromethyl malonic acid		*"1,1-cyclohexane dicarboxylate"
25		*difluoro malonic acid		*ditrifluoroethyl malonic acid
				*dichloro malonic acid

Table 5 identifies some representative α and β -amino carboxylic acids, i.e. Arms, of interest for the preparation of macrocyclic tetraamides, either in parent, hidden, or protected/activated form.

Table 5 - The Amino Carboxylic AcidsDerivatives of α -Amino Carboxylic Acids (5ac)

	*R(-)-2-amino-2-methyl butanedioic acid	*S(-)-2-amino-2-methyl-4-pentenoic acid monohydrate
5	*S(+)-2-amino-2-methyl butanedioic acid	*2-amino-2-norbornane carboxylic acid
	*S(+)-2-amino-2-methyl butanoic acid hydrate	*R(-)-2-amino-2-phenylbutyric acid
	*2-amino-2-methyl butyric acid	*1-aminocyclopropane-1-carboxylic acid
	*2-amino-2-methyl glutaric acid	*1-aminocyclobutane-1-carboxylic acid
10	*R(-)-2-amino-2-methyl-3-hydroxy propanoic acid	*1-aminocyclopentane-1-carboxylic acid (cycloleucine)
	*S(+)-2-amino-2-methyl-3-hydroxy propanoic acid	*1-aminocyclohexane-1-carboxylic acid
15	*S(+)-2-amino-2-methyl-4-phosphonobutanoic acid	*S(+)-2-amino-2-methyl-3-phenyl propanoic acid
	* α,α -diphenyl glycine	* α -phenyl alanine ((+/-)- α -methyl- α -phenyl glycine)
	* α -amino-isobutyric acid (α -methyl alanine)	*S(+)-2-amino-2-phenylbutyric acid
20	*cis-1-amino-3-(2-phosphonoacetyl) cyclobutane-1-carboxylic acid	

Derivatives of β Carboxylic Acids (6ac)

*†The β -amino acids derived from 2-amino-benzoic acid (anthranilic acid) are quite oxidatively robust

25	Registry #	Compound containing 2-amino-benzoic acid	Registry #	Compound containing 2-amino-benzoic acid
	118-92-3	*†(o-amino-benzoic acid, anthranilic acid)	118-92-3	*†(o-amino-benzoic acid, anthranilic acid)
	619-17-0	*4-nitro-	3177-80-8	*3-methoxy-
30	616-79-5	*5-nitro-	6705-03-9	*5-methoxy-
	4389-45-1	*3-methyl-	394-31-0	*5-hydroxy-

	2305-36-4	*4-methyl-	4920-81-4	*3-hydroxy-hydrochloride
	2941-78-8	*5-methyl-	446-32-2	†4-fluoro-
	4389-50-8	*6-methyl-	446-08-2	†5-fluoro-
5	609-86-9	*3,5-diiodo-	434-76-4	†6-fluoro-
	5653-40-7	*4,5-dimethoxy-		*4-chloro-5-sulfamoyl-
	50419-58-4	*3,4-dimethyl-	6388-47-2	†3-chloro-
	14438-32-5	*3,5-dimethyl-	89-77-0	†4-chloro-
	15540-91-7	*3,6-dimethyl-	635-21-2	†5-chloro-
10	2789-92-6	†3,5-dichloro-	2148-56-3	†6-chloro-
	609-85-8	*3,5-dibromo-		*3-bromo-5-methyl-
		*3,5-dibromo-6-fluoro-	1765-42-0	†3,4,5,6-tetrafluoro-
			61948-85-4	*3,4,5-trimethoxy-
15	Registry #	Other β-amino carboxylic acids	Registry #	Other β-amino carboxylic acids
			5959-52-4	†3-amino-2-napthoic acid
20	5434-20-8	*3-amino-pthalic acid	5345-47-1	*2-amino-nicotinic acid (2-aminopyridine-3-carboxylic acid)
	614-19-7	*β-amino-hydrocinnamic acid (D,L-3-amino-3-phenyl-propionic acid)	82-24-6	†1-amino-anthraquinone-2-carboxylic acid
25	52834-01-2	*2-amino-4,6-dimethyl-3-pyridinecarboxylic acid hydrochloride	1664-54-6	*3-amino-3-phenyl-propionic acid
	54711-21-6	*5-amino-4-cyano-1-methyl-pyrazole	50427-77-5	*5-amino-1-phenylpyrazole-4-carboxamide
30	698-29-3	*4-amino-5-cyano-2-methyl pyrimidine	72-40-2	*5(4)-aminoimidazole-4(5)-carboxamide hydrochloride
35		*4-amino-5-cyano-2-methoxy pyrimidine	68302-09-0	*2-amino-7-ethyl-5-oxo-5H-[1]benzopyrano[2,3-b]pyridine-3-carbonit

			rile
	41680-34-6	*3-aminopyrazole-4-carboxylic acid	22603-53-8 *2-amino-3,5-dinitrobenzonitrile
5	87550-19-4	*3,6-dinitrophthalic acid pyridine salt	*5-amino-4-cyano-1-(4-chlorophenyl)pyrazole
	5424-01-1	*3-amino pyrazine-2-carboxylic acid	*5-amino-4-cyano-1-(4-nitrophenyl)pyrazole
	10312-55-7	*2-amino terephthalic acid	16617-46-2 *5-amino-4-cyano pyrazole
10			6375-47-9 *3-amino-4-acetamido anisole

Table 6 identifies some representative diamines, i.e. Bridges, of interest for the preparation of macrocyclic tetraamides, either in parent, hidden, or protected/activated forms. Amine and protected/activated or hidden amine functionalities are used interchangeably.

15

Table 6 - The DiaminesDerivatives of 1,2-Aryl Diamines (5aa)

*all of the aryl diamines shown are comparatively robust towards oxidation.

Registry #	Compound containing o-Phenylenediamine	Registry #	Compound containing o-Phenylenediamine
20	Substituents = 0		Substituents = 0
	95-54-5 †(1,2-Benzenediamine)	95-54-5	†(1,2-Benzenediamine)
	No. of Unique Substituents = 1		No. of Unique Substituents = 1
	18645-88-0 †3-fluoro-	21745-41-5	†3-chloro-
25	367-31-7 †4-fluoro-	95-83-0	†4-chloro-
	153505-39-6 †3,4-difluoro-	1668-01-5	†3,4-dichloro-
	2369-29-1 †3,5-difluoro-	5233-04-5	†3,5-dichloro-
	2369-30-4 †3,6-difluoro-	21732-93-4	†3,6-dichloro-

5	76179-40-3	[†] 4,5-difluoro-	5348-42-5	[†] 4,5-dichloro-
	168966-54-9	[†] 3,4,5-trifluoro-	30064-28-9	[†] 3,4,5-trichloro-
	363-74-6	[†] 3,4,6-trifluoro-	1962-10-3	[†] 3,4,6-trichloro-
	2993-07-9	[†] 3,4,5,6-tetrafluoro-	877-12-3	[†] 3,4,5,6-tetrachloro-
	1575-36-6	[*] 3-bromo-	34446-43-0	[*] 3-iodo-
	1575-37-7	[*] 4-bromo-	21304-38-1	[*] 4-iodo-
	1575-38-8	[*] 3,5-dibromo-	144793-03-3	[*] 3,6-diiodo-
	69272-50-0	[*] 3,6-dibromo-	76179-43-6	[*] 4,5-diiodo-
	49764-63-8	[*] 4,5-dibromo-		
10		No. of Unique Substituents = 2		No. of Unique Substituents = 2
	75293-95-7	[*] 4-bromo-5-chloro-	132915-81-2	[†] 3-chloro-4-fluoro-
	16429-44-0	[*] 5-bromo-3-chloro-	153505-33-0	[†] 3-chloro-5-fluoro-
	172215-94-0	[*] 3-bromo-4,5-dichloro-	139512-70-2	[†] 4-chloro-5-fluoro-
15	98138-54-6	[*] 4-bromo-3,5-dichloro-	153505-43-2	[*] 5-chloro-3-iodo-
	74908-80-8	[*] 3,5-dibromo-4-chloro-	153505-34-1	[†] 3-chloro-4,5-difluoro-
	115440-10-3	[*] 3-bromo-5-fluoro-	170098-84-7	[†] 4-chloro-3,5-difluoro-
	153505-37-4	[*] 4-bromo-5-fluoro-	156425-14-8	[†] 4-chloro-3,5,6-trifluoro-
20	153505-35-2	[*] 3-bromo-4,5-difluoro-	153505-47-6	[*] 4,5-dichloro-3-iodo-
	156425-12-6	[*] 4-bromo-3,5,6-trifluoro-	18225-92-8	[†] 3,4,6-trichloro-5-fluoro-
			153505-45-4	[*] 5-fluoro-3-iodo-

25	Registry Number	Additional 1,2-Benzenediamines	Registry Number	Additional 1,2-Benzenediamines
		[*] 4,5-dimethyl- [†] 4,5-dinitro-		[*] 4-methyl- [†] 4-nitro-
30	88580-71-6	[*] 4,5-dimethoxy- [*] 4,5-diamino-		[*] 4-methoxy- [*] 4-amino-
		[†] 4,5-diacetamido-		[†] 4-acetamido-

		[†] 4,5-ditrifluoromethyl-		[†] 4-trifluoromethyl-
		[†] 4,5-dicyano-		[†] 4-cyano-
		[*] 4,5-dihydroxy	615-72-5	[*] 4-hydroxy (3,4-diamino-phenol)
5			59649-56-8	[*] 3-hydroxy (2,3-diamino-phenol)
		Other n,n+1-Diamines		Other n,n+1-Diamines
		[†] 1,1,2,2-tetramethyl ethylene diamine	452-58-4	[*] 2,3-diamino pyridine
10	7598-26-7	[*] 2-amino-3-nitro-5-methyl pyridine	54-96-6	[*] 3,4-diamino pyridine
	6635-86-5	[*] 2-amino-3-nitro-4-picoline (2-amino-4-methyl-3-nitro pyridine)		[*] 2-amino-3-nitro-5-bromo-pyridine
15	82039-90-5	[*] 5-amino-4-nitro-imidazole		[*] 4-amino-5-nitro-6-chlor-pyrimidine
		[*] 5-amino-3-methyl-4-nitro-isoxazole		[*] 2-amino-3-nitro-9-fluorenone
20		[*] 5-amino-1,3-dimethyl-4-nitro-pyrazole	7598-26-7	[*] 2-amino-3-nitro-5-methyl-pyridine
	6632-68-4	[*] 6-amino-1,3-dimethyl-5-nitroso-uracil		[*] 4-amino-5-nitroso-uracil
	22603-53-8	[*] 2-amino-3,5-dinitro-benzonitrile	1672-48-6	[*] 6-amino-5-nitroso-2-thio-uracil
25	3531-19-9	[*] 1-amino-2,4-dinitro-6-chlorobenzene		[*] 2-amino-5-bromo-3-nitro-pyridine
	5442-24-0	[*] 4-amino-2,6-dihydroxy-5-nitro-pyrimidine	33685-60-8	[†] 9,10-dinitro-anthracene
30		[*] 4-amino-2,6-diketo-1,3-dimethyl-5-nitroso-pyrimidine		[*] 6,7-dinitro-2,3-diphenoxy-quinoxaline
		[†] 1,2-dinitro-tetramethyl-benzene	35975-00-9	[†] 5-amino-6-nitro-quinoline
35		[*] cis-1,2-diamino-1,2-dimethyl-cyclohexane	771-97-1	[†] 2,3-diamino-napthalene
		[*] cis-1,2-diamino-1,2-dimethyl-cyclopentane	938-25-0	[†] 1,2-diamino-napthalene

5	36023-58-2	*5,6-diamino-2,3-dicyano-pyrazine	39070-63-8	*3,4-diamino-benzophenone
	5440-00-6	*5,6-diamino-1,3-dimethyl-uracil	68836-13-5	*6,7-dinitro-quinoxaline
		*5,6-diamino-3-methyl-uracil		*5,6-dinitro-quinoxaline-2,3-dione
	1758-68-5	*1,2-diaminoanthraquinone	2379-57-9	*6,7-dinitro-quinoxaline-2,3-dione
	6968-22-5	*3-amino-4-nitro-benzoic acid	52057-97-3	*3,4-diamino-5-hydroxypyrazole sulfate
10	13754-19-3	*4,5-diamino-pyrimidine	1672-50-0	*4,5-diamino-6-hydroxypyrimidine
	3240-72-0	*4,5-diamino-uracil (5,6-diamino-uracil)		

15 Derivatives of n,n+2 Diamines (6aa)

Registry #	n,n+2-diamines	Registry #	n,n+2-diamines
20	*2-amino-2-(2-aminophenyl)-propane		*2,4-diamino-2,4-dimethyl-pentane-3-one
	*1,3-diamino-1,3-dimethylcyclohexane		*2,4-diamino-2,4-dimethyl-pentane
	479-27-6		*1,8-diaminonaphthalene

The list of n, n+2-Diamines is significantly shorter than for the other derivatives, in large part because the syntheses of the required n,n+2 diamines are more complex than for the n, n+1 diamines.

25 Some specific examples of bridge, arm and linker starting materials are shown in Table 7. In each case the amide bonds have been retrosynthetically decomposed to form an amine equivalent (amine, nitro, azide, isocyanate, etc. *see* Table 1) and a carboxylic acid equivalent (acid, ester, acyl chloride, nitrile etc. *see* Table 1).

The bridges and linkers of Table 7 conserve local two fold symmetry while all of the arms shown lead to 5-membered chelate rings.

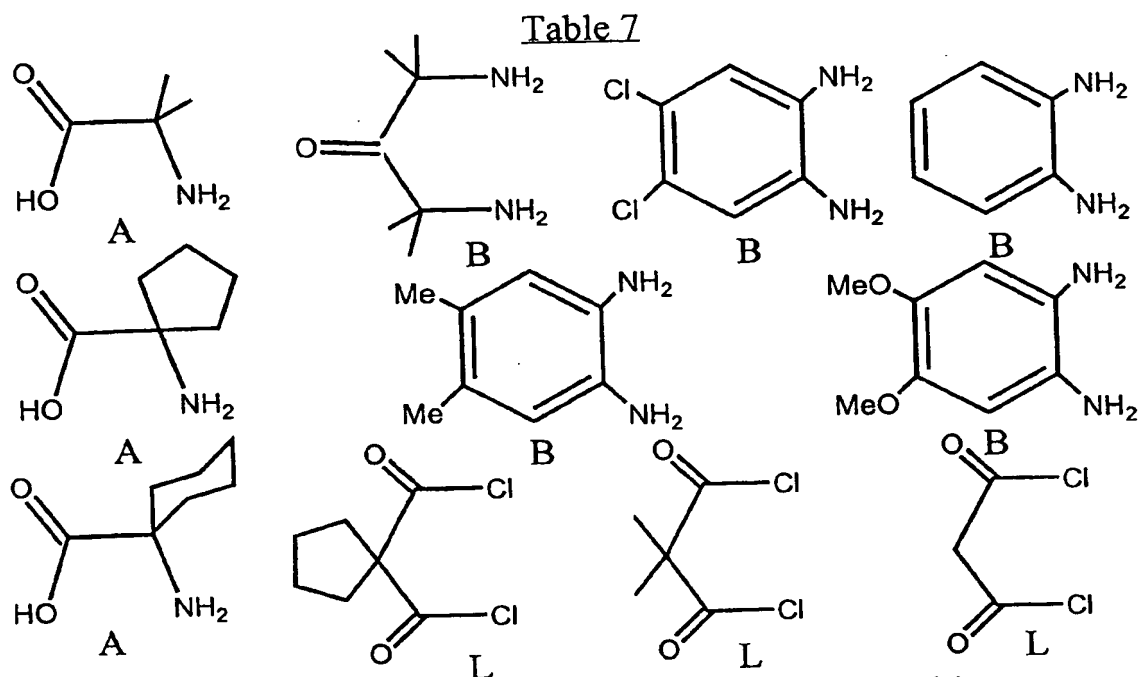


Table 7 shows some specific Bridge, B, Arm, A, and Linker, L, starting materials.

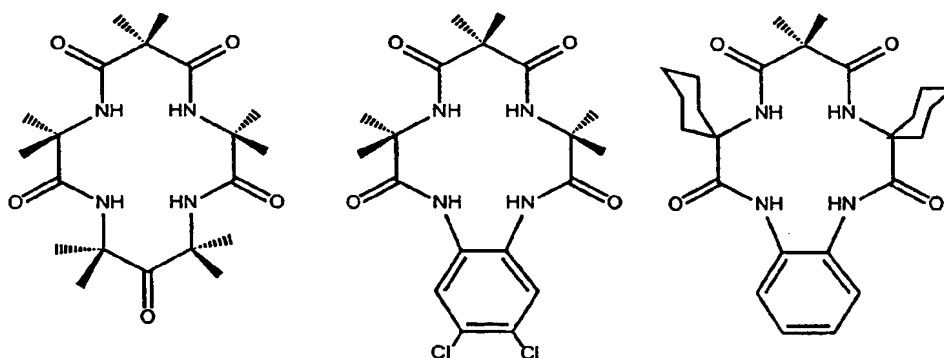
The R groups do not participate in the synthesis reaction so numerous variations are possible. However, as discussed above, to form the oxidatively robust compound and catalyst, there are certain restrictions placed on the R groups. There is considerable evidence that hydrogen atom abstraction occurs between the linker's R substituents and the axial ligand bound to the central metal atom of the ultimate chelate system. This abstraction then is believed to lead to oxidative degradation, as shown in the proposed mechanism of Fig. 1.

Molecular models revealed that, in a boat conformation of the macrocyclic complex's six-membered linker ring, the methylene H-atoms of the ethyl groups can reach to the oxygen atom of an Fe-oxo complex. This and other data lend support to the mechanism shown in Fig. 1 and explain the parameters of the R₁ and R₂ substituents. To avoid the H-atom abstraction and consequent degradation, the R groups of the preferred macrocyclic compounds should be those that will slow down the H-atom abstraction reaction and thereby slow down oxidative degradation. To accomplish this, the R₁ and R₂ groups of the compound of the present invention are those that have a good bond strength, are unreactive, or which are not accessible to the axial ligand, such as sterically or conformationally hindered groups.

Any one or any combination of these attributes may be employed. The latter option can be achieved by reducing the conformational freedom of the R_1 and R_2 groups so that they simply are not close enough to react. As used herein good C-H bond strength means more than 94 Kcal.mol⁻¹ or more than 85 Kcal.mol⁻¹ for sterically inaccessible C-H bonds.

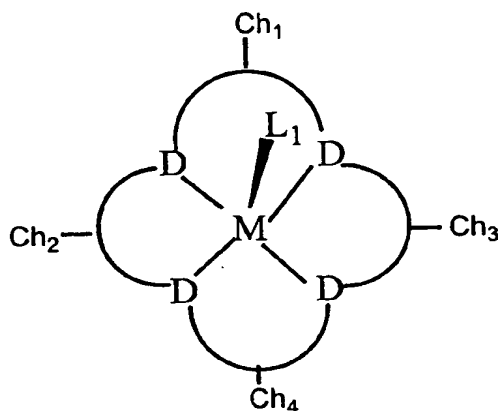
5 The malonate linker portion is the most sensitive part of the macrocycle ligand. Preferred R groups on the linker include methyl, halogen, hydrogen, CF₃ and a spiro-cyclobutyl, spiro-cyclopropyl, spiro-cyclopentyl or spiro-cyclohexyl ring in place of R_1 and R_2 .

10 There is considerably more freedom in choosing the R substituents for the arm portions than for the linker because of the robustness of this portion of the compound which may reflect the inability of a five-membered ring to adjust to bring oxidizable C-H groups in contact with an axial oxo ligand. Thus, the R groups of the a and b amino carboxylic acid can also be chosen to tailor the substituents of the resulting macrocycle to the desired end use. The macrocycle may be symmetrical or asymmetrical. For asymmetrical macrocycles,
15 two different amino acid starting materials are used and the resulting macrocycles are a mixture of symmetrical and asymmetrical versions. The two versions can be separated by known separation techniques. A few examples of the compounds of the present invention are shown below.

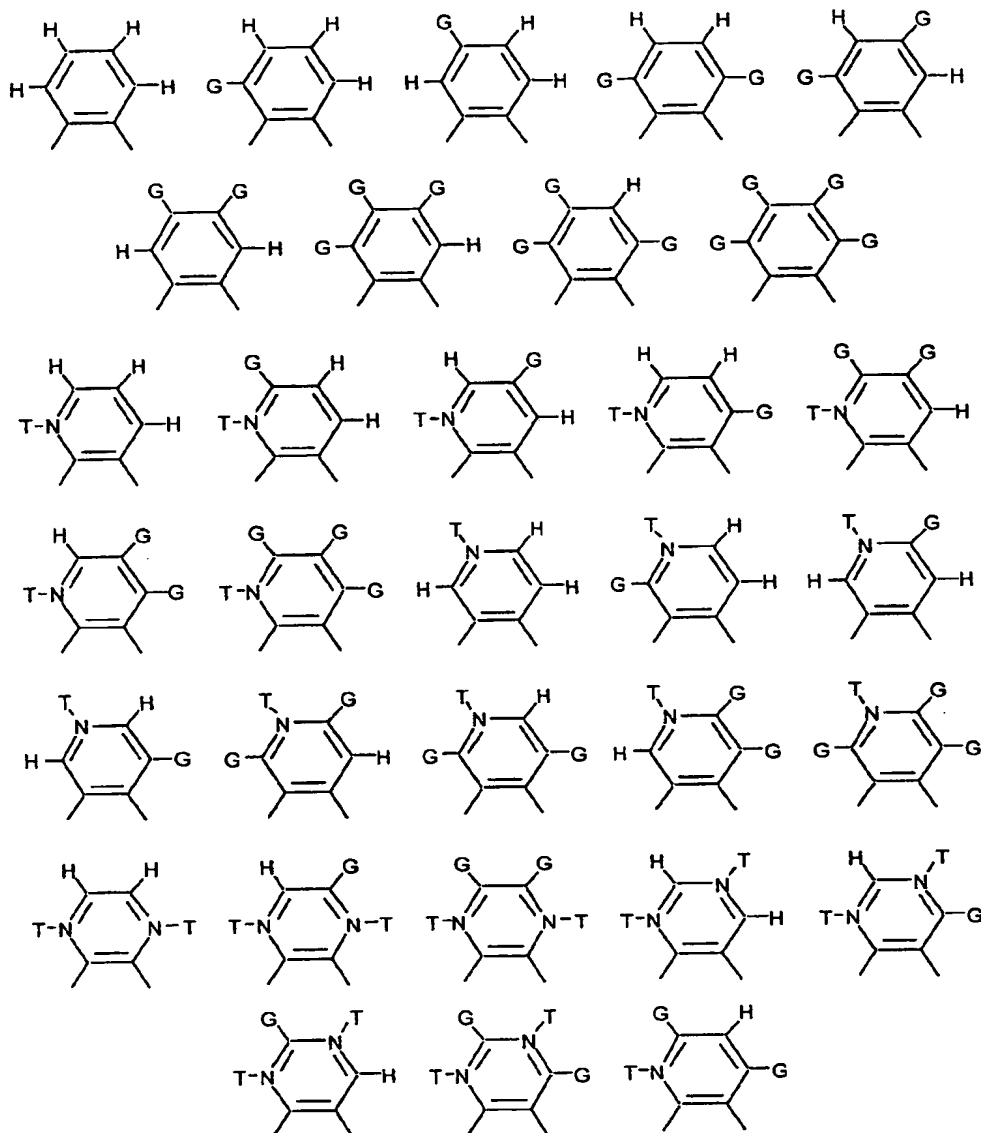


20 Once the macrocyclic tetradentate ligand has been prepared, the macrocyclic compound may be complexed with a wide range of metal ions, preferably a transition metal

from groups 3-12 of the Periodic Table, and most preferably a group 6, 7, 8, 9, 10 or 11 metal, to form a chelate complex of the formula



- 5 wherein M is the metal, D is a donor atom selected from the group consisting of N, O and NR_D, and D is a donor atom selected from the group consisting of N, O and NR_D, and R_D is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkoxy, phenoxy, halogen, halogenated alkyl, halogenated aryl, halogenated alkenyl, halogenated alkynyl, perhaloalkyl, perhaloaryl, a substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted
- 10 cycloalkenyl ring, a substituted or unsubstituted saturated heterocyclic ring, and a substituted or unsubstituted unsaturated heterocyclic ring. L₁ is any labile ligand. Ch₁, Ch₂, Ch₃ and Ch₄ are oxidation resistant components of the chelate system described above (corresponding to the Y groups of compound 1) which are the same or different and which form five- or six-membered rings with the adjacent DMD atoms.
- 15 The R substituents on adjacent carbons of Ch₁ form a constituent selected from the group consisting of



Each T is the same or different and is an unoccupied position, hydrogen, alkyl or haloalkyl.

Each G is the same or different and comprises halogen, hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, alkylaryl, phenoxy substituents, amino, substituted amino, nitro,

5 alkoxy, aryloxy and combinations thereof.

Complexation is achieved by the following method. The macrocyclic ligand is dissolved in a supporting solvent, usually THF, and deprotonated by treatment with a base, preferably lithium bis-trimethylsilylamide, lithium di-isopropyl amide, t-butyl lithium, n-butyl lithium, or phenyl lithium. Any base that removes the protons at the metal complexing

site, *e.g.*, the amide N-H protons of an amide containing compound, will suffice.

Noncoordinating organic soluble bases are preferred. After the ligand is deprotonated, a metal ion is added. The resulting intermediate, a comparatively low valent ligand metal species, is then oxidized. The oxidation step is preferably performed with air, chlorine, bromine, or benzoyl peroxide to produce the metal chelate complex usually as a lithium salt. Metathesis of the resulting complex to form a tetraalkyl ammonium, tetraphenyl phosphonium or bis(triphenylphosphoranylidene) ammonium (PPN) salt tends to yield metal chelate complexes that are easier to purify as compared to the lithium ion containing complexes. The purified metal chelate complex, can then be used to catalyze oxidation reactions.

If the complex is then combined with a strong O-atom transfer oxidant, preferably a peroxide, such as hydrogen peroxide, t-butyl hydroperoxide, cumyl hydroperoxide or a peracid, a ligand metal IV, V or VI oxo intermediate is produced. When oxidatively robust substituents have been employed to generate the ligand framework, the robust, high oxidation state oxo containing species apparently form as reactive intermediates. It is believed that these high valent oxo containing species are the active transfer agents in catalyzing a number of oxidation reactions.

When a low valent metal species is exposed to a peroxide or other [O] containing oxidant the metal attracts and binds the oxygen from the oxidant. Depending on the metal, the bond between the metal and the oxygen will be very strong or may be only strong enough to remove the oxygen from the oxidant for subsequent transfer to another constituent.

If the metal is a metal III ion, the resulting oxo species will in general be a metal V ion. If the metal is a metal IV ion, the resulting oxo species will in general contain a metal VI ion or a metal V complex with a second oxidation site on the ligand, *i.e.*, a ligand cation-radical. The combined stabilizing effect of the macrocyclic ligand and the participation of the d electron count at the metal center in controlling the degree of bonding to an oxo ligand tends to favor early transition metal complexes forming very strong oxygen-metal bonds to yield stable oxides. The middle and later transition metals tend to remove the oxygen from the oxidant and bind the oxo ligand to form a reactive intermediate. In the metal ligand system produced by the new synthetic method, the middle and later transition metals tend to promote the transfer of oxygen.

In addition to its stabilizing effect, the ligand also exerts influence on the metal properties. By controlling the metal, the electron density of the macrocycle, the charge on the complex, and the bond strength/bond order to the coordinated oxo ligand, the metal ligand complex can be fine tuned to achieve a complete range of oxygen transfer abilities, from stable oxides to high valent oxidation catalysts.

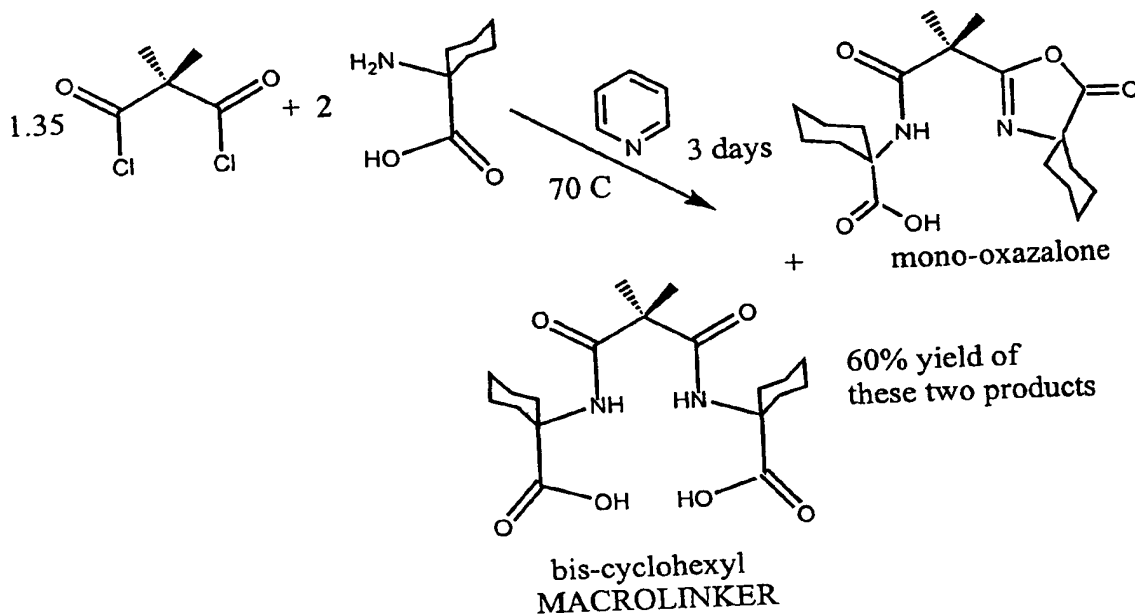
In the preferred embodiment, the axial ligand, L_1 , is labile because it occupies its position relative to the metal until the chelate system is introduced into a solution containing an oxidant. The labile ligand will dissociate and will be replaced by the oxidant, most generally an O-atom transfer agent, but also any general oxidant that can serve to activate the metal ion to perform catalysis. Preferred labile ligands include, but are not limited to, the Cl^- anion, halide ions in general, CN^- , H_2O , OH^- , ROH , NH_3 , or any amine, carboxylate, phenol or phenoxide, pyridine, ether, sulfoxide, ketone, or carbonate. The oxidation site in the metal complexes of aromatic-ring containing macrocycles can be manipulated by the choice of axial ligands as well as by the ring substituents.

Macrocycles with spiro-cyclohexyl substituents have been prepared and found to render the macrocycle very hydrophobic and, remarkably, soluble in pentane and other light saturated aliphatic solvents. Long chain substituents, such as a dodecyl chain, or phospholipid chain will render the macrocycle soluble in membranes.

The spiro-cyclobutyl, -cyclopropyl, -cyclopentyl and -cyclohexyl derivatives are sterically hindered and has slower reaction rates than the other preferred substituents, so the normal synthesis of the amide intermediate of the first step of the method of the invention is altered.

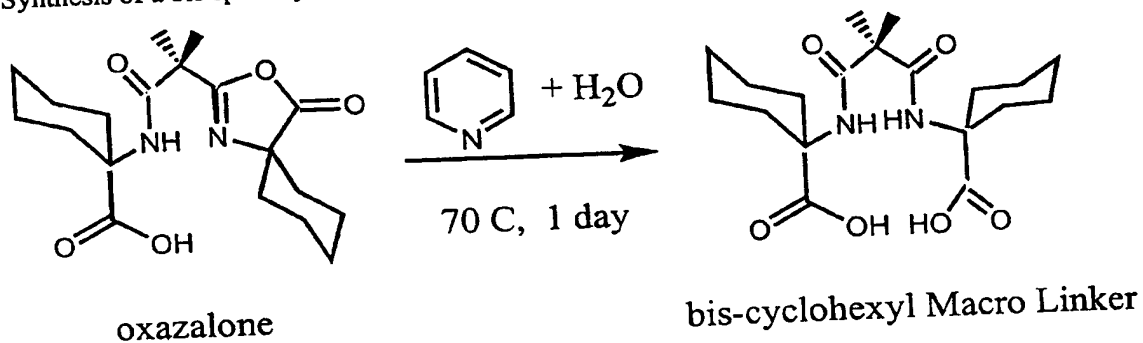
Synthesis of the bis spiro-cyclohexyl macro linker intermediate was accomplished by adding acylating agent dropwise in multiple aliquots, preferably three, separated in time.

Twelve hour intervals preferably followed by extended reaction periods produced the best results. Without the extended reaction periods, the yield was lower. The reaction sequence is shown in the sequences below. Cyclohexane can be used to separate the oxazalone form of the macro linker away from the other reaction products, or water can be added to hydrolyze the oxazalone in situ. Hydrolysis of the intermediate oxazalones provides an increased yield of the desired bis cyclohexyl macro linker product.



Sequence 12

Synthesis of a bis spiro-cyclohexyl macro linker.



Sequence 13

5

Hydrolysis of a hydrophobic oxazalone

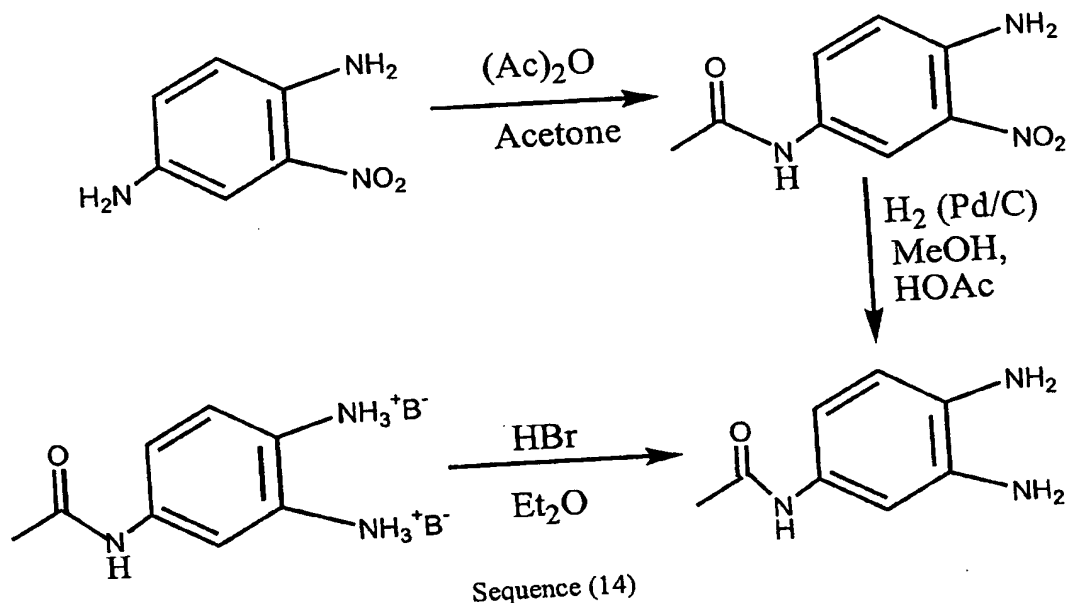
The cyclohexyl-containing macro linker is then ready for ring closure in the same manner as other intermediates of the invention. However, due to the enhanced stability of the spiro-cyclohexyl containing macrocyclic intermediates, separation of the macrocycle from reaction by-products differs from other preferred ring closing constituents. Typically, the crude macrocyclic product is extracted into an organic solvent, such as CH_2Cl_2 . The CH_2Cl_2 solution is washed with acids and bases to remove the impurities and side products that contain acidic and basic functionalities and to hydrolyze any oxazalone containing

intermediates. The cyclohexyl amide containing macrocycle is not well purified by the usual acid/base washes yielding instead an approximately 1:1 mixture of the bis cyclohexyl oxazalone and bis-cyclohexyl amide containing macrocycle. Pentane extraction of the mixture yields a clean separation. The macrocycle is insoluble and isolated as a powder, while the pentane soluble fraction can be evaporated to yield large crystals of the bis cyclohexyl oxazalone.

It has been observed that addition of an excess of the substituted malonyl dichloride improves the yield of macro linker with an optimum ratio of about 2 moles of amino acid to 1.35 to 1.5 moles of the substituted malonyl dichloride. The product mixture includes the macro linker and a mono-oxazalone form of the macro linker which can be readily hydrolyzed to yield additional product. The yield of the method is improved significantly if water is excluded from the reaction solution during ring closure reactions.

Pyridine diamines can also be utilized. The prior art azide synthetic route, which includes a reduction step that also reduces the pyridine ring, does not yield a macrocyclic compound having a pyridine bridge. Amino pendant variations would also be tedious to synthesize by the prior art synthesis methods. The amino pendant variations are of considerable interest because they permit the macrocyclic compound or metallocomplex to be tethered to a support, such as a polymer or sand, or to other molecules or substrates having functional groups which will covalently bond with the amine. Groups which covalently bond with amines are well known in the art and include in complexed form, for example, alkyl amines, amides, sulphonamides, imines, and other hidden or protected/activated forms, *see* Table 1.

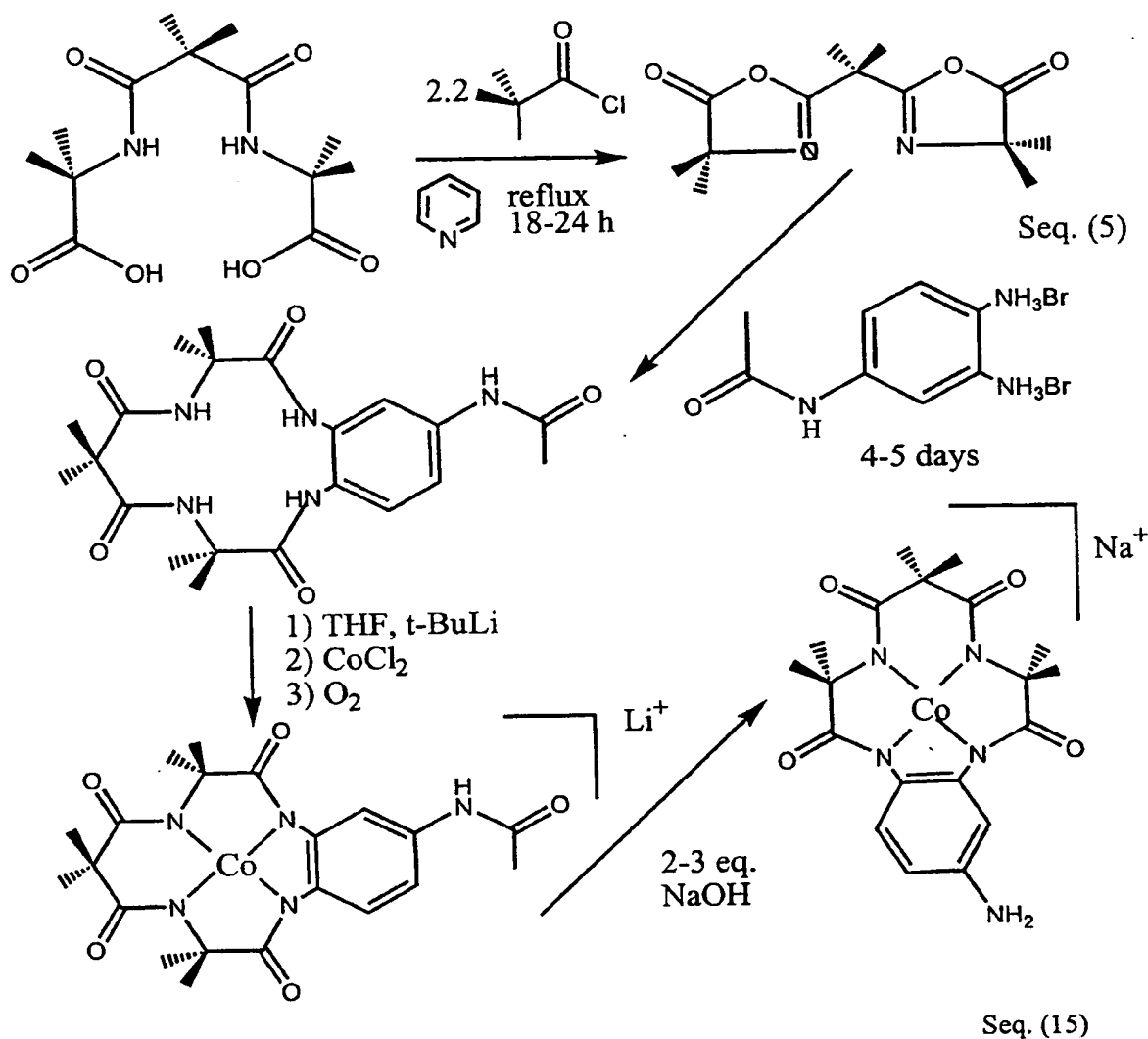
The synthesis of the aryl amino pendant macrocycle proceeds generally as in Sequences 14 and 15.



Synthesis of 1,2-Diamino-4-Acetamidobenzene (dihydrobromide)

The sequence includes the strategic and selective introduction of a protected amino group (an acetamide) onto the aryl diamine group (Bridge). The protected form of the bridge, an acetamido diamine is then suitable for ring closure via the standard diamine + intermediate linker synthetic routes described herein. An extended ring closure time is required to achieve macrocyclization and is attributed to unfavorable hydrogen bond formation between the attached oxazalone and the acetamido group, which would be expected to slow down the desired macrocyclization reaction.

Once the protected amino pendant macrocycle has been synthesized as in sequence 15, it can be metallated with cobalt. Removal of the acetyl protecting group then yields a macrocyclic cobalt complex that is ready to be attached to a support. Best results to date have been obtained by reacylating the pendant amino group with acryloyl chloride to yield an amide linked vinyl pendant macrocycle.



Synthesis of an amino pendant macrocyclic cobalt complex

This may then be copolymerized with a twenty fold excess of various acryloyl monomers to yield an acrylic polymer that contains a macrocyclic cobalt complex as a sidechain approximately every 20 residues, shown schematically in Fig. 5.

By anchoring the macrocyclic metal complex to a polymer or some other support, the metal may be reclaimed and recycled according to the system shown schematically in Fig. 4. Environmentally toxic metals, for example Cr^{VI} can be replaced by more environmentally benign oxidation reagents, such as Co^{IV} or Co^{III}L^I species, where L^I refers to a ligand centered oxidation.

Referring to Fig. 4, following the desired oxidation process, the anchored oxidant can be recycled via collection and reoxidation with a primary oxidant, such as hypochlorite, bromine or by electrolysis. Use of anchored macrocyclic metal species is expected to provide a viable method to significantly reduce the levels of discharge of toxic spent metallic species into the environment. The polymer bound oxidant system of Fig. 4 serves as an example of a recyclable "Green" oxidation reagent.

EXPERIMENTAL SECTION

Syntheses of Oxidatively Robust Tetradentate Ligand.

Materials. All solvents and reagents were reagent grade (Aldrich, Aldrich Sure-Seal, Fisher) and were used as received. Microanalyses were performed by Midwest Microlabs, Indianapolis, IN.

Electrochemical Measurements. Cyclic voltammetry was performed under N_2 in a three compartment cell using a glassy carbon disk working electrode ($A \sim 0.0078 \text{ cm}^2$ or 0.071 cm^2), a Pt wire counter electrode, and a sodium chloride saturated calomel electrode (SSCE) as reference. CH_2Cl_2 (Aldrich Sureseal) or CH_3CN (dried over CaH_2) were employed as solvents with a supporting electrolyte of $[Bu_4N][ClO_4]$ (0.1 M, Fluka, vacuum dried 24 h $^\circ C$) or $[Bu_4N][PF_6]$ (0.1 M, Fluka puriss). A Princeton Applied Research Model 273 Potentiostat/Galvanostat controlled with a Compudyne 486DX computer was used and current/voltage curves were recorded on a Graphtec Model WX1200 X-Y recorder, or using a Princeton Applied Research Model 173/179 potentiostat/digital coulometer equipped with positive feedback IR compensation, a Model 175 universal programmer, and a Houston Instruments Model 2000 X-Y recorder. For some experiments, ferrocene (Fc) was added as an internal potential standard at the conclusion. Formal potentials were calculated as the average of anodic and cathodic peak potentials and are reported vs NHE. Peak-to-peak separation of the Fc^+/Fc couple was similar to that of the iron compound couples in all cases. Plots of peak current vs. the square root of scan speed over the range 20-500 $mV \text{ s}^{-1}$ were found to be linear for all couples.

Mass Spectrometry. Electrospray ionization mass spectra were acquired on a Finnigan-MAT SSQ700 (San Jose, CA) mass spectrometer fitted with an Analytica of Branford electrospray interface. Electrospray voltages of 2400-3400 V were utilized. Samples were dissolved in either acetonitrile or dichloromethane at concentrations of approximately 10 pmol/ml and

were introduced into the ESI interface prior to data acquisition by direct infusion at a flow rate of 1 ml/min. Positive ion electron impact ionization (70 eV) MS experiments were performed on a Finnigan-MAT 4615 quadrupole mass spectrometer in conjunction with an INCOS data system. The ion source temperature was 150°C and the manifold chamber temperature was 100°C. Sample introduction was by means of a gas chromatograph or a direct insertion probe. Positive ion fast atom bombardment mass spectra were acquired on a Finnigan-MAT 212 magnetic sector instrument in combination with an INCOS data system. The accelerating voltage was 3 kV and the ion source temperature was approximately 70°C. An Ion Tech saddle field fast atom gun was employed with xenon at 8 keV. Thioglycerol was utilized as the FAB matrix. Positive ion electron impact ionization (70 eV) MS/MS experiments were performed on a Finnigan-MAT TSQ/700 tandem quadrupole mass spectrometer. Sample introduction was by means of a direct insertion probe. The ion source was maintained at 150°C and the manifold chamber was held at 70°C. Collision-induced dissociation (CID) was achieved by introducing argon into the center rf-only collision octapole until the pressure in the manifold reached $0.9\text{--}2.5 \times 10^{-6}$ Torr. The nominal ion kinetic energy for CID product ions was < 35 eV (laboratory reference). High resolution data were obtained on a JEOL JMS AX-505H double focusing mass spectrometer in the EB configuration using a resolution of 7500. Sample introduction was by means of a gas chromatograph or direct insertion probe. During mass spectral acquisition, perfluorokerosene was introduced into the ion source by means of a heated inlet. Exact mass assignments were obtained by computer-assisted interpolation from the masses of perfluorokerosene. GC/MS conditions: column, 20 m x 0.25 mm DB-1701 (J & W Scientific); carrier gas, helium with a linear velocity of 40 cm/sec; injector, 125°C; column temperature, 35 °C for 3 min, followed by an increase at 10°C/min to 100°C; injection, split mode, appx. 50:1 ratio.

Spectroscopic Methods. 300 MHz ¹H NMR spectra and 75 MHz ¹³C NMR spectra were obtained on an IBM AF300 instrument using an Oxford Superconducting magnet system, data acquisition was controlled by Bruker software. Infrared spectra were obtained on a Mattson Galaxy Series 5000 FTIR spectrometer controlled by a Macintosh II computer. UV/vis spectra were obtained on a Hewlett Packard 8452A spectrophotometer driven by a Zenith Z-425/SX computer. Conventional X-Band EPR spectra were recorded on a Bruker ER300 spectrometer equipped with an Oxford ESR-900 helium flow cryostat. Mössbauer

spectra were obtained on constant acceleration instruments and isomeric shifts are reported relative to an iron metal standard at 298 K. In order to avoid orientation of polycrystalline samples by the applied magnetic field, the samples were suspended in frozen nujol.

Syntheses of Diamines not Readily Available Commercially

Example 1

A. 1,2-Diamino-4,5-Dimethoxy Benzene from 1,2-Dimethoxy Benzene (veratrole)

1,2-Dinitro-4,5-Dimethoxy Benzene: Veratrole was doubly nitrated according to the procedure of Drake et al, in "Synthetic Antimalarials. Some Derivatives of 8-Aminoquinoline", J. Amer. Chem. Soc., 1536, Vol. 68 (1946). Nitric acid (68.3 g, conc.) was added (dropwise, 1 h) to a well stirred solution of veratrole (48.3 g, 350 mmol, $d = 1.084$) in glacial acetic acid (1450 mL) initially cooled to 15°C. The mixture needs to be held below 40°C but above 10°C by cooling and proper regulation of the rate of addition of the acid. Considerable mononitroveratrole separated out. Stirring was continued and additional nitric acid (212.7 mL, fuming) was added (dropwise, 1 h) while the temperature of the solution was held below 30°C. As the second nitration proceeded the mono nitroveratrole dissolved and when all the acid had been added, the solution was clear. The nitration mixture was allowed to stand for two hours and was then poured into ca. 1.5 L of ice/cold water. The precipitated dinitro compound was filtered, washed copiously with water until free from acid ($pH > 5$), and recrystallized directly from a minimum of hot EtOH (600 mL). The yield of 1,2-Dimethoxy-4,5-dinitrobenzene was 69.0 g (87%). Characterization: m.p. 129.5-130.5 °C. 1H NMR ($CDCl_3$) δ [ppm]: 7.35 (s, 2H, ArH), 4.02 (s, 6H, OCH_3). IR nujol ν [cm^{-1}]: 3124 (s, w, Aryl CH), 3073 (s, w, Aryl CH), 1592 (s, str, Aryl ring stretch), 1535 & 1518 (s, str, $ArNO_2$). Anal. Calcd. For $C_8H_8N_2O_6$: C, 42.11; H, 3.53; N, 12.28. Found: C, 42.12; H, 3.54; N 12.33.

1,2-Diamino-4,5-Dimethoxy Benzene: 1,2-Dimethoxy-4,5-dinitrobenzene (10 g, 43.8 mmol) was reduced to 1,2-Dimethoxy-4,5-diamino benzene in acidic MeOH (175 mL + 2 eq. of mineral acid, (i.e., 10 mL of conc. HBr)) by catalytic hydrogenation using 10% Pd/C catalyst (24-36 h, 20-22 psi of H_2 was consumed from the reservoir). If more than 2 eq. of HBr are

added initially the Pd/C catalyst is found to be strongly inhibited. After hydrogenation was complete an additional 4-5 eq. of conc. mineral acid was added to protect the material from aerial oxidation and the mixture rotary evaporated to yield a red/purple oil. The crude material was purified by adding a small volume of Abs. EtOH, then pouring the slurry into a 600 mL volume of ice cold Et₂O, with storage in the freezer overnight. The red-purple product was collected by filtration, air dried briefly then stored in a dessicator to complete the drying process. Prolonged exposure of the diamine salt to air/water causes a green color to develop which appears indicative of irreversible oxidation. Hydrogenation yield was »90%. Characterization of the red-purple 1,2-Dimethoxy-4,5-Diaminobenzene (dihydrobromide salt hydrate). ¹H NMR (d⁵ pyridine) δ [ppm]: 10.35 (s, br, 7.5 H, H₂O/py.HBr/R-NH₂, rapidly exchanging), 7.35 (s, 2 H, ArH), 3.60 (s, 6 H, ArOCH₃). IR (nujol/NaCl) ν [cm⁻¹]: 3085 (br, OH), 2557 (s, str, ArNH₃⁺), 1623 (s, w, asymmetric NH₃⁺ bend/Aryl ring stretch), 1539, 1519 (s, m, symmetric NH₃⁺ bend). (Anal. Calcd. for C₈H₁₂N₂O₂) (HBr)₂ (H₂O)_{0.66}: C, 28.09; H, 4.52; N, 8.19. Found: C, 27.82; H, 4.18; N, 8.37. Independent confirmation of hydration was obtained from IR and NMR spectroscopy.

Preparation of the anhydrous sulfate salt of 1,2-Diamino-4,5-Dimethoxy Benzene has been reported by Nakamura, M. et. al. in "Fluorimetric Determination of Aromatic Aldehydes with 4,5-Dimethoxy-1,2-Diaminobenzene" *Anal. Chim. Acta.* (1982), 134, p.39-45 as follows: 1,2-Diamino-4,5-Dimethoxybenzene (2 g) was dissolved in EtOH (20 mL) and mixed with H₂SO₄ (conc., ca. 2 mL). The product was recrystallized from EtOH to almost colorless needles (yield ca. 2 g). Anal. Calcd for C₈H₁₀O₂N₂S: C, 36.1; H, 5.3; N, 10.5. Found: C, 35.85; H, 5.6; N, 10.4.

B. 1,2-Diamino-4-acetamidobenzene from
1,4-diamino-2-nitrobenzene (2-Nitro-1,4-phenylenediamine)+

1-Amino-2-nitro-4-acetamidobenzene: 1,4-diamino-2-nitrobenzene (2-nitro-1,4-phenylenediamine) was selectively acetylated according to the method of McFarlane et. al, J. Chem. Soc. Perkin Trans., 691 (1988) incorporated herein by reference. The amine meta to the nitro group is readily acetylated using acetic anhydride in acetone (the amine ortho to the nitro group is strongly deactivated). The yield of 1-Amino-2-nitro-4-acetamidobenzene (2-nitro-4-acetamido aniline) was > 90%. Characterization: ¹H NMR (CD₃OD) δ [ppm]: 8.3

(m, 1 H, ArH), 7.5 (M, 1 H, ArH), 6.9 (M, 1 H, ArH), 2.1 (s, 3 H, acetyl CH₃) in good agreement with McFarlane. IR (nujol/NaCl) $\tilde{\nu}$ [cm⁻¹]: 3470 (s, str, HOAc), 3340-3150 (m, m/str, acetamide ArNH + ArNH₂), 1661 (s, str, acetamide CO), 1643 (s, str, H bonded acetamide CO), 1592 (s, m/w, aryl stretch), 1547 (s, str, ArNO₂) & 1512 (s, m ArNO₂). Anal. (Dried at 80 °C) Calcd for C₈H₉N₃O₃: C, 49.23; H, 4.65; N, 21.53. Found: C, 49.36; H, 4.55; N, 21.31.

1,2-Diamino-4-acetamidobenzene: 1-Amino-2-nitro-4-acetamidobenzene was reduced to 1,2-Diamino-4-acetamidobenzene in acetic acid (HOAc)/MeOH using catalytic hydrogenation over a 10% Pd/C catalyst. The material was isolated as the dihydrochloride salt. Yield > 90%. Characterization: ¹H NMR (CD₃OD) δ [ppm]: 6.94 (m, 1 H, ArH), 6.68 (m, 1 H, ArH), 6.62 (m, 1 H, ArH), 2.1 (s, 3 H, acetyl CH₃). IR (nujol/NaCl) $\tilde{\nu}$ [cm⁻¹]: 3348 (s, str, acetamide ArNH), 3226-3100 (m, m, ArNH₂), 2588 (s, br, str, ArNH₂), 1649 (s, str, acetamide CO), 1623 (s, str, H bonded acetamide CO). Anal. (Dried at 80 °C) Calcd for C₈H₁₃N₃OCl₂ · (HCl/H₂O)_{0.1}: C, 39.45; H, 5.50; N, 17.25; Cl, 30.57. Found: C, 39.39; H, 5.53; N, 17.32; Cl, 30.37. Presence of solvate HCl/H₂O was confirmed by IR, and is consistent with the constant boiling 36.5-38% HCl used to generate the hydrochloride salt.

C. 2,4-Diamino-2,4-Dimethyl Pentanone from 2,4-dimethylpentanone 2,4-Dibromo-2,4-dimethylpentanone:

To 2,4-dimethylpentanone (85 mL, 68.5 g, 0.60 mol) in CCl₄ or 1,2 Dichloroethane (1 L) was added N-bromo-succinimide (NBS, 240 g, 1.35 mol, 2.26 equiv). The mixture was heated under reflux, and benzoyl peroxide (ca 20 mg) was added to the refluxing mixture. While the solution was heated under reflux (24 h), a pale orange solid (succinimide) floated to the surface of the halogenated solvent, while unreacted NBS remained at the bottom. Benzoyl peroxide was repeatedly added to the refluxing mixture (ca 20 mg; 12-24 hr intervals) until no NBS was visible, usually the reaction was complete after 24 hours. When the reaction was complete, the solids were collected by filtration and discarded, the halogenated solvent/Br₂ was removed from the mother liquor under reduced pressure, leaving a pale yellow oil. To remove residual halogenated solvent, 95% EtOH (100 mL) was added, solvents were again removed under reduced pressure, and a yellow slightly impure oil resulted (159.99 g, 0.59 mol, 98%). ¹H NMR (CDCl₃): 2.1 (s). IR

(neat/NaCl) n [cm^{-1}]: 3375 (s, w, impurity OH), 3014, 2978, 2933 (s, str, CH), 2858 (s, w, CH), 1701 (s, str, ketone CO).

2,4-Diazido-2,4-dimethylpentanone: A solution of 2,4-Dibromo-2,4-dimethylpentanone prepared as above or purchased from Lancaster Synthesis (89.8 g, 0.33 mol) in EtOH (1.2 L, 95%) was added to a solution of NaN₃ (Caution!, 47.2 g, 0.726 mol, 2.2 equiv) in water (0.6 L). The solution was heated under reflux (16 h) to give a pale orange solution. The EtOH was removed under reduced pressure until the solution became cloudy. The cloudy aqueous solution was extracted, still warm, with pentane (500 mL) three times, and the combined extracts were dried over Na₂SO₄ and concentrated to 300 mL under reduced pressure. Glacial acetic acid (100 mL) was then added, and the remaining pentane was removed under reduced pressure. This workup was required to remove any excess NaN₃, since the product is exposed to Pd/C in the next step, and care should be taken to avoid the formation of heavy metal azides (due to the risk of explosion). The solvent was removed from a small sample under reduced pressure to give a neat oil (< 20 mg) for spectroscopic characterization: ¹H NMR (CDCl₃): 1.54 (s). IR (neat) n [cm^{-1}]: 2115 (RN₃), 1720 (ketone CO). It should be noted, for safety, that the organic azides produced in this and related azide based syntheses are never isolated in concentrated forms or as solids in quantities greater than 20 mg.

2,4-Diamino-2,4-dimethylpentan-3-one: Glacial acetic acid (50 mL) was added to the HOAc solution of the dialkyl azide formed in the previous step, and this solution was added to 10% Pd/C (2.7 g). The mixture was hydrogenated at 50 psi (1 week) in a Parr hydrogenator. Because the reaction evolves one N₂ molecule for every H₂ molecule absorbed, the bomb was evacuated and repressurized 10 times with H₂ to 50 psi. (H₂ from the high pressure reservoir is not efficiently consumed.) The charcoal was removed by filtration, and HOAc was removed under reduced pressure. After HBr was added (48%, 76 mL), the mixture was dissolved in EtOH. The volatiles were removed under reduced pressure to yield a tan solid, which was washed with a mixture (200 mL) of THF (50%), EtOH (45%), and conc. HBr (5%) or with a mixture of THF (95%) and conc. HBr (5%). The resulting white powdery product was the dihydrobromide salt of 2,4-Diamino-2,4-dimethylpentan-3-one (56.2 g, 48% from 2,4-Dibromo-2,4-dimethylpentanone). Additional product may be collected from washings that have been pooled from several different preparations. The product must be

stored as the dihydrobromide or dihydrochloride salt to protect the amines from oxidative degradation. Characterization: ^1H NMR ($\text{CDCl}_3/\text{DMSO}-d_6$) of 2,4-diamino-2,4-dimethylpentan-3-one . 2 HBr: 8.62 (6H, s, br, NH_2), 1.77 (12 H, s, Me). IR (free base, nujol mull) $n[\text{cm}^{-1}]$: 3460-3160 (RNH_2), 1690 (ketone CO). Anal. (Dried at 80 °C) Calcd for $\text{C}_7\text{H}_{16}\text{N}_2\text{O}$. (HBr) $_2$: C, 27.47; H, 5.93; N, 9.15; Br, 52.22. Found: C, 27.43; H, 5.91; N, 9.11; Br, 52.46.

Syntheses of Macrocyclic Tetradentate-Donor Ligands

Example 2

Macro Linker Intermediate (A-L-A) synthesis, from α -methyl alanine and dimethyl malonyl dichloride (a Tetramethyl Dimethyl substituted intermediate).

10 Hexamethyl (HM) Intermediate

Place a two-neck flask (1 L) fitted with a pressure equalizing addition funnel (250 mL) and a septum under N_2 . Add α -amino isobutyric acid (i.e. α -methyl alanine) (20.62 g, 0.2 mol) and dry pyridine (250 mL, dried over 4 Å mol sieves) to the flask and heat 55-65°C with stirring, then add dimethyl malonyl dichloride (17.8 mL, 0.135 mol) dissolved in dry pyridine (100 mL, dried over 4 Å mol sieves) to the addition funnel. Add the contents of the addition funnel (dropwise, 1 h) to the reaction and allow the acylation to proceed (60-70°C, 30-36 h) under N_2 or with a drying tube fitted. Once the acylation is complete, quench the reaction by adding H_2O (30 mL) and stirring (60-70°C, 24 hrs). Reduce the solvent volume on the rotary evaporator to give an oil, then add HCl (conc., ca. 25 mL) to a final pH of 2-3. Set the hot solution in the refrigerator (4°C, 15 h), and collect the resulting product by frit filtration, and wash thoroughly with acetonitrile (2 x 100 mL). The air-dried white product, (16.5 - 19.8 g, 45-60% yield) should be stored in a desiccator. This product is usually pure enough for ring closure reactions, but recrystallization may occasionally be required. Characterization: ^1H NMR (d' pyridine, δ [ppm]): 9/2-9.8 br s, 2 H (carboxylic OH), 8.23 s, 2 H (amide), 1.87 s 12 H (CH_3), 1.74 s 6 H (CH_3). IR (nujol/NaCl) $n[\text{cm}^{-1}]$: 3317.0 (amide NH); 1717.9 (carboxylic CO); 1625.7 (amide CO). Anal. (dried at 100 °C) Calcd. for $\text{C}_{13}\text{H}_{22}\text{N}_2\text{O}_6$; C 51.63, H 7.34, N 9.27. Found; C 51.64, H 7.35, N 9.33.

Example 3

Large Scale, Macro Linker Intermediate (A-L-A) synthesis, from α -methyl alanine and diethyl malonyl dichloride (a TMDE substituted intermediate).

- If a large scale synthesis is desired, a two-neck flask (2 L, RB + Claisen) should be fitted with a pressure equalizing addition funnel (250 mL) and septa, and placed under N_2 . Add α -aminoisobutyric acid (i.e. α -methyl alanine) (90.3 g, 0.9 mol) (or any α - or β - amino described herein), cannulate anhydrous pyridine (1.4 L, sure seal) into the flask and heat the reaction mix to 45-55°C and stir. Cannulate Pyridine (100 mL, sure seal) and then dimethyl malonyl dichloride (104.4 mL, 0.61 mol) into the addition funnel. Add the contents of the addition funnel (dropwise, 3-4 h) to the reaction, remove the addition funnel, and allow the acylation to proceed (55-65°C, 120-130 h) under N_2 . Once the acylation is complete, quench the reaction by adding H_2O (100 mL) and stirring (60-70°C, 24-36 hrs). Reduce the solvent volume on the rotary evaporator to give an oil, then add HCl (conc., ca. 110 mL) to a final pH of 2-3. Set the hot solution in the refrigerator (4°C, 15 h), and collect the resulting product by frit filtration, and wash thoroughly with acetonitrile (700 mL, 150 mL) by stirring in an erlenmeyer flask. Crush the air-dried white product (87.9 g, 60% yield), in a mortar and pestle and store in a dessicator. The large scale reaction amide intermediate product is more likely to need recrystallization before use in ring closure reactions.

Example 4

Recrystallization of HM Intermediate

Crude intermediate from Example 2 or 3 (50.4 g, 0.153 mol) in H₂O (slightly less than 500 mL, deionized) is dissolved by adding Na₂CO₃ (16.2 g, 0.153 mol) in three aliquots slowly and carefully to avoid excessive frothing. Stir good and heat mildly. Bring the solution to a boil, filter and acidify with HCl (conc., 30 mL, 0.36 mol). Allow the solution to cool (overnight, 4°C) and filter the precipitate off and wash with acetonitrile (250 mL). The air dried product (38.8-45.4 g, recryst. yield 77-90%) should be stored in a dessicator.

Macrocyclization Reactions

Several synthetic routes for the preparation of macrocyclic tetradentate ligands have been developed. The organic azide based route is described in Uffelman, E.S., Ph.D. Thesis, California Institute of Technology (1992) and Kostka, K.L., Ph.D. Thesis Carnegie Mellon University (1993). Examples of several synthetic routes for the preparation of amide containing macrocycles using a new synthetic method follow.

15 Phosphorus Trichloride Coupling

Phosphorus trichloride coupling of the amide intermediate reaction product to aromatic 1,2-diamines yields macrocyclic tetraamides safely, cheaply and in high yield. Two distinct variations of the PCl₃ coupling method are useful, the differences relate to the order of addition and choice of reagents utilized. These methods are applicable to the preparation of a wide variety of different macrocycles with different electronic substituents present on the bridge diamine, or steric substituents present on the amide intermediate, primarily because of the parallel incorporation of the macro linker type of amide intermediates into all of the syntheses.

Example 5

A. Macrocycle Synthesis via PCl_3 Coupling

A long neck flask (250 mL) is charged with the amide intermediate of Examples 2-4, (10 mmol) and a stir bar and then baked in the oven (80-100°C, 30-45 mins). The hot flask is placed under N_2 , aryl diamine (10 mmol) is added and anhydrous pyridine (50 mL, sure seal) cannulated in. The flask is heated (50-60°C) and PCl_3 (d = 1.574 g/mL, 1.72 mL, 20 mmol) syringed in as quickly as possible without excessive refluxing. This is an exothermic reaction, so caution should be used. The temperature is then increased to reflux or just below reflux (100-115°C) and the reaction allowed to proceed under N_2 (48 h). After the acylation is complete, the contents of the flask are acidified with HCl (1 eq., ca. 60 mL) to a final pH »2. The mixture is transferred to an erlenmeyer (water is used to rinse the flask) and stirred with CH_2Cl_2 (300 mL, 2-3 h), then extracted with additional CH_2Cl_2 (2 x 150 mL). The combined organic layers are washed with dilute HCl (0.1 M, 2 x 100 mL) followed by dilute aqueous Na_2CO_3 (2 x 5g/100 mL). The organic solvents are removed on the rotary evaporator to yield crude product (30%). The weight of crude product is usually equivalent to the initial weight of diamine.

B. Macrocycle Synthesis via PCl_3 Coupling

A long neck flask (250 mL) is charged with MgSO_4 (5 g), a stir bar, aryl diamine (10 mmol) and pyridine (50 mL, dried over 4 Å mol sieves) then placed under N_2 . PCl_3 (d = 1.754 g/mL, 1.72 mL, 20 mmol) is added via syringe and the mixture brought to reflux for 30 mins, an orange/yellow precipitate forms. The mixture is cooled somewhat, an amide intermediate (10 mmol) is added, then the mixture is refluxed under N_2 (115°C, 48 h). After the acylation is complete, the contents of the flask are acidified with HCl (1 eq., ca. 60 mL) to a final pH »2. The mixture is transferred to an erlenmeyer and stirred with CH_2Cl_2 (300 mL, 2-3 h), then extracted with additional CH_2Cl_2 (2 x 150 mL). The combined organic layers are washed with dilute HCl (0.1 M, 2 x 100 mL) followed by dilute Na_2CO_3 (2 x 5g/100 mL). The

organic solvents are removed on the rotary evaporator to yield crude product (30%). The weight of crude product is usually equivalent to the initial weight of diamine.

Note: For larger scale macrocyclization reactions, the ring closure times are increased to 4-5 days at reflux, and most of the pyridine present at the end of the reaction is removed via

5 rotary evaporation prior to acidification.

Example 6

HM-DCB from HM Intermediate + DCB Diamine

1,2-Diamino-4,5-Dichlorobenzene (1.77 g, 10 mmol) was utilized as the diamine with Hexa Methyl amide intermediate (3.02 g, 10mmol) in the PCl_5 method A or B macrocyclization
10 reaction. The crude macrocycle (1.33g, 30%) was recrystallized from a minimum of hot n-propanol by evaporation, 1st crop recrystallization yield was 60%. Characterization: ^1H NMR d [ppm]: 7.69 (s, 2 H, ArH), 7.39 (s, 2 H, amide NH), 6.44 (s, 2 H, amide NH), 1.58 (s, 12 H, arm methyls), 1.53 (s, 6 H, malonate methyls), small n-propanol peaks were noted. IR (nujol/NaCl) ν [cm^{-1}]: 3503 (s, br, m-w, n-propanol OH), 3381 (sh, m, amide NH), 3338 (s,
15 str, amide NH), 1689 (s, str, amide CO), 1643 (s, str, amide CO). Anal. Calcd. for $\text{C}_{19}\text{H}_{24}\text{N}_4\text{O}_4\text{Cl}_2 \cdot (\text{C}_3\text{H}_8\text{O})_{0.2}$: C, 51.70; H, 5.57, N 12.30% Found C, 51.69; H, 5.63; N, 12.33%.

Oxazalone Coupling Reactions

Oxazalone coupling of the amide intermediate to aromatic diamines also yields tetradentate macrocycles safely, cheaply and in high yield, but with less sensitivity to additional
20 functional groups. The macrocycles able to be formed via the PCl_5 coupling route can also be manufactured via the oxazalone coupling route. In addition, the lesser sensitivity to additional functional groups has opened up the preparation of macrocyclic ligands with additional functional groups designed to confer new properties on the resulting metal complexes. Specific examples include the incorporation of reactive groups (such as amine or
25 vinyl groups) attached in a pendant fashion to the aryl ring of the macrocycle allowing for covalent attachment of the preformed macrocycles to some (polymeric) substrate.

Example 7

Macrocycle Synthesis via Oxazalone Method

A long neck flask (250 mL) is charged with amide intermediate (3.3 g, 10 mmol), a stir bar and then baked in the oven (80 - 100°C, 30-45 mins). The hot flask is fitted with a septum and placed under N₂. Anhydrous pyridine (50 mL, sure seal) is cannulated in and heating commenced while trimethyl acetyl chloride (i.e. pivaloyl chloride) (22 - 24 mmol) is added via syringe. The temperature is increased to reflux or just below reflux (100-115°C) and the reaction allowed to proceed under N₂ (22-26 h) being careful to avoid cross contamination from other reactions on the N₂ line. The reaction goes from a clear pale yellow to a yellow-brown color. After oxazalone formation is complete[†], the aryl diamine (8-10 mmol) is added either as a neat solid or via large bore cannula as a slurry in anhydrous pyridine, or dissolved and degassed under N₂ in anhydrous (sure seal) pyridine, if head space and solubility constraints can be satisfied. The ring closure reaction is refluxed for a further 48-72 hours (longer times for larger scales) under N₂ without cross contamination from other reactions. The mixture will usually turn brownish black. Once the acylation is complete, the reaction is quenched by adding H₂O (30 mL) and stirring at reflux (100°C, 22-26 hrs). The mixture is cooled and transferred to an RB flask (500 mL) using a minimum of H₂O to rinse the long neck flask. The solvent is removed via rotary evaporation to yield the crude product mixture as an oily tan to brownish black solid. It should be noted that, functional groups permitting, the crude product mixture can be taken up in CH₂Cl₂ and washed with dilute aqueous HCl and dilute aqueous Na₂CO₃. Removal of the organic solvent at reduced pressure then yields the normal macrocyclic product familiar from the PCl₅ coupling reactions and suitable for direct recrystallization as detailed previously to yield pure macrocyclic product.

[†]Pumping an aliquot down and redissolving in dry d⁵ pyridine yielded a dominant species (>80% bis oxazalone after 24 h at reflux) with ¹H NMR δ [ppm]: 2.10 (q, 4 H, methylene CH₂'s), 1.38 (s, 12 H, RCH₃), 0.85 (t, 6 H, ethyl CH₃'s). Addition of water to the NMR sample regenerated the normal amide intermediate spectrum after about 20 h at RT.

Example 8

TMDE-AcB from TMDE Intermediate + AcB Diamine via oxazolones.

This macrocycle is the protected form of an amino pendant macrocycle which can be attached to a range of different supports through amide formation between the substrate and the pendant amino group. Due to what is speculated to be formation of an unfavorable hydrogen bond, the ring closure reaction requires lengthy reflux times in order to achieve macrocyclization. 1,2-Diamino-4-acetamidobenzene dihydrochloride (9 mmol) was employed as the diamine in an oxazalone ring closure reaction. The macrocyclization time was increased (reflux, 5 days), followed by the normal quenching reaction and acid base workup to yield a mixture of a triamido containing macrocyclic imidazole and the desired tetraamido macrocycle. Further purification was by silica gel chromatography (1" x 4-5") using acetonitrile as the eluant. Alternatively, the crude product can be purified by recrystallization from hot ethanol, chloroform or dichloroethane. Yield 15-20% from diamine. Characterization: ¹H NMR (CD₃CN) δ [ppm]: 8.31 (s, 1 H, aryl acetamide NH), 7.72 (m, 1 H, ArH), 7.55 (s, 1 H, aryl amide NH), 7.44 (s, 1 H, aryl amide NH), 7.30 (m, 2 H, ArH), 6.86 (s, 2 H, alkyl amide NH), 2.05 (q, 4 H, ethyl CH₂'s), 2.01 (s, 3 H, acetyl CH₃), 1.49 (d, 12 H, RCH₃'s), 0.82 (t, 6 H, ethyl CH₃'s). IR (nujol/NaCl) ν [cm⁻¹]: 3368 (s, m, amide NH), 3319 (s, m, amide NH), 3291 (sh, m, amide NH), 3268 (s, str, amide NH), 1678 (sh, m, amide CO), 1667 (s, str, amide CO), 1656 (s, str, amide CO), 1639 (sh, m, amide CO), 1608 (s, m, aryl ring/amide). Anal. Calcd for C₂₃H₃₃N₅O₅ · (H₂O)_{1.25}: C, 57.31 H, 7.42 N, 14.53 Found: C, 57.02; H, 7.15; N, 14.33. Presence of solvate H₂O was confirmed by ¹H NMR and IR

Example 9

Synthesis of a peralkylated macrocycle (MAC*), or TMDM-DMP from the TMDM intermediate + 2,4-Diamino-2,4-dimethyl-Pentan-3-one (DMP) via the Oxazalone Route.

The PCl₃ route to H₄[MAC*] (TMDM-DMP) fails to produce appreciable amounts of macrocycle due to what is speculated to be unfavorable complex formation between the diamine ketone functionality and the phosphorus reagent. Unlike the PCl₃ route, which is heterogeneous, the oxazalone route to H₄[MAC*] is a homogeneous solution method which

simplifies the application of diagnostic techniques such as ^1H NMR to diagnose causes of synthetic failure. Reaction of TMDM bis oxazalone with DMP diamine in dry pyridine fails to form any amides (by NMR analysis). Since the oxazalone route is insensitive to ketone functionalities, the failure to form amides was attributed to acid salt formation of the alkyl amine functionality, the alkyl diamine is 3-4 pK_a units more basic than pyridine while aryl diamines have pK_a 's close to that of pyridine. Therefore, a more basic high boiling solvent (triethylamine, tripropylamine, diethylaniline) may be used to increase the amount of amide formation. For amine containing solvents, the presence of water and impurity amines is problematic considering the low solubility of the reactants. Addition of a lewis acid drying agent was found to be beneficial. An appreciable yield of $\text{H}_4[\text{MAC}^*]$ can be obtained (2-3% macrocyclization yield, unoptimized) from the reaction (1 step) of TMDM bis oxazalone with DMP alkyl diamine in refluxing tripropylamine + CaO . Isolation of the product should be by fractional recrystallization from toluene in combination with ^1H NMR analysis.

The highest possible yield of $\text{H}_4[\text{MAC}^*]$ from alkyl diamine via the prior art method of Uffelman (4 steps from the alkyl diamine) is 8-10%. $\text{H}_4[\text{MAC}^*]$ can be obtained in appreciable yield via the oxazalone route.

Synthesis of Chelate Complexes

The compounds labeled 2, 3, 4 and 5 in the following examples are the dimethyl counterparts of those illustrated in Fig. 6.

Example 10

$[\text{Et}_4\text{N}]_2$ and $[\text{Et}_4\text{N}]_3$. [the tetraethylammonium salts of iron(III) chloro TMDM-DCB monoanion and iron(III) aquo TMDM-DCB monoanion respectively].

The parent macrocyclic tetradentate compound of any of the foregoing examples (525 mg, 1.1 mmol) is dissolved in tetrahydrofuran (40 mL, Aldrich) under N_2 . Tert-butyllithium under N_2 (2.6 mL, 4.4 mmol, 1.7 M in 2,4-dimethylpentane, Aldrich) is added to the solution under N_2 at -108°C . Ferrous chloride (anhydrous, 155 mg, 1.2 mmol, Alfa) is added and the solution is warmed to room temperature with stirring (16 h), to yield a precipitate, an air sensitive $\text{Fe}^{\text{II}}\text{L}$ complex. Air is admitted through a drying tube (2 h), and the solid is collected and washed with CH_2Cl_2 (2 x 10 mL). The resulting powder is dried under reduced pressure. Yield: 595 mg ($\gg 93\%$). Because of variable solvation and limited solubility, the lithium salt should be converted to the tetraethylammonium salt for further use. The lithium salt (595

mg) in CH_3OH (50 mL) is loaded on an ion exchange column (Dowex® 50X2-100, 25 g, 2 cm x 12.5 cm) that is presaturated with $[\text{Et}_4\text{N}]^+$ cations, and the band is eluted with CH_3OH (100 mL). The solvent is removed under reduced pressure. The residue is suspended in CH_2Cl_2 (20 mL) and the mixture filtered. The solvent is removed from the mother liquor under reduced pressure giving a hygroscopic glassy residue of $[\text{Et}_4\text{N}]\text{2}$ that may be used without further purification. IR (Nujol/ NaCl , cm^{-1}): 1619 (n(CO)amide), 1575 (n(CO)amide), 1534 (n(CO)amide). Careful purification of an iron(III) starting material is more conveniently approached by dealing with the axial aqua monoanionic complex rather than this axial chloro dianionic complex. $[\text{Et}_4\text{N}]\text{2}$ (550 mg, ca. 0.7 mmol) was dissolved in CH_3CN (50 mL). Silver tetrafluoroborate (140 mg, 0.7 mmol) is dissolved in CH_3CN (2 mL) and added to the solution which is stirred (1 h). The AgCl precipitate is filtered off and the solvent removed under reduced pressure. The resulting $[\text{Et}_4\text{N}]\text{3}$ is further purified by elution through a silica gel column (8% MeOH in CH_2Cl_2). The solvent is removed under reduced pressure and the product is recrystallized from H_2O .

15

Example 11

$[\text{Et}_4\text{N}]\text{4}$. [the tetraethylammonium salt of iron(IV) chloro TMDM-DCB monoanion].

$[\text{Et}_4\text{N}]\text{2}$ (500 mg, ca. 0.6 mmol) was dissolved in CH_2Cl_2 (30 mL). Ammonium cerium(IV) nitrate (10.3 g, 18.3 mmol) is added to the solution and the mixture stirred (2 h). The solid cerium salts are removed by filtration. The product is obtained by removing the solvent under reduced pressure and drying under vacuum.

20

Example 12

Synthesis of $[\text{Ph}_4\text{P}]\text{5}$ [the tetraphenylphosphonium salt of iron(IV) cyano TMDM-DCB monoanion] from $[\text{Et}_4\text{N}]\text{4}$ [the tetraethylammonium salt of iron(IV) chloro TMDE-DCB monoanion] and NaCN .

25

$[\text{Et}_4\text{N}]\text{4}$ [the tetraethylammonium salt of iron(IV) chloro TMDM-DCB monoanion] (225 mg, 0.33 mmol) is suspended in H_2O (10 mL). Sodium cyanide (140 mg, 2.85 mmol) is dissolved in H_2O (10 mL) and added to the suspension and the mixture sonicated (Branson 1200, 0.5 h). The mixture is filtered and the blue product is precipitated by adding PPh_4Cl

[tetraphenylphosphonium chloride] dissolved in water (600 mg, 1.6 mmol, 10 mL, Aldrich). The precipitate is collected and washed with H₂O (2 x 10 mL). The material should be extracted from the silica gel with CH₃CN:CH₂Cl₂ (1:1, 60 mL). The solvent is removed under reduced pressure and the residue dissolved in CH₂Cl₂ (3 mL) and filtered. Addition of pentane (150 mL) will give a powder (90 mg, 0.10 mmol)

Example 13

The Synthesis of [Ph₄P]5 [the tetraphenylphosphonium salt of iron(IV) cyano TMDM-DCB monoanion] from Nitrile Cyanide Sources.

[Ph₄P]5 [the tetraphenylphosphonium salt of iron(IV) cyano TMDM-DCB monoanion] can be formed in the presence or absence of base. In the absence of base, the color fades as the solvent is removed in the workup procedures. Therefore, product isolation to obtain the solid is best carried out in the presence of added base at a pH range of 9-10. The following reaction will yield 5 with each of CH₃CN, CD₃CN, CH₃CH₂CN and (CH₃)₂CHCN as the solvent substrates. Base is not added to the catalytic reactions described.

Example 14

The Synthesis of [Ph₄P]5 in the Presence of Base.

[Et₄N]3 (160 mg, 0.23 mmol) is dissolved in the chosen nitrile solvent (6 mL). See Example 13. Tetraethylammonium hydroxide base is added (20 wt %, 0.370 mL, 0.52 mmol, Aldrich), then t-butyl hydroperoxide (90%, 0.605 mL, 5.4 mmol, Aldrich) is added dropwise with stirring (20 min) resulting in a blue solution. The remaining nitrile is removed under reduced pressure, leaving an oily residue which is dissolved in H₂O (15 mL) and filtered. The material is precipitated from the filtrate by addition of an aqueous solution of PPh₄Cl (800 mg, 2.1 mmol, Aldrich, 10 mL). The blue precipitate is collected and washed with H₂O (2 x 10 mL). Yield: 130 mg, 0.15 mmol (65%). Further purification was carried out as described in the [Ph₄P]5 section, Example 12.

Example 15

1-[2-((E)-2-butenyl-2-ethylamido)-2-methylpropanamido]-2-[5,5-dimethylhydantoin]-4,5-dichlorobenzene (i.e. a ligand decomposition product).

[Et₄N]⁺2 (130 mg, 0.13 mmol) is dissolved in CH₃CN (5 mL, Aldrich). A 90% solution of t-butyl hydroperoxide (0.445 mL, 4 mmol, Aldrich) is added slowly (3 min). The reaction mixture is stirred (25 min) and then all liquids removed under reduced pressure. The residue is dissolved in CH₂Cl₂ and loaded onto a preparative thin layer chromatography (TLC) plate (Silica gel GF, 1000 mm, 20 cm x 20 cm) and eluted with a 15% CH₃CN/ 85% CH₂Cl₂ solvent mixture. The product band is detected under UV irradiation at an R_f value of 0.3. The portion of the silica that contains the product is removed from the preparative plate and the product should be extracted with CH₂Cl₂:CH₃CN (1:1). The solution is filtered and the solvent removed under reduced pressure. A solid is obtained by dissolving the residue in CH₂Cl₂ (3 mL) followed by addition of pentane (150 mL). This is collected by filtration and washed with pentane (2 x 10 mL).

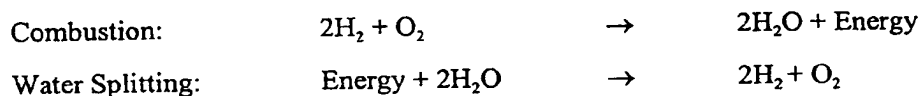
Some examples of specific applications of various embodiments of the macrocyclic compounds of the present invention are disclosed in co-pending patent application Serial No. 08/684,670 of T. Collins et al., entitled "Metal Ligand Containing Bleaching Compositions" filed on July 22, 1996 and in application Serial No. 08/804,776 filed February 24, 1997, of T. Collins et al. entitled "Metal Ligand Containing Bleaching Compositions," both of which are incorporated herein by reference. Other examples are set forth below.

Applications of High Valent Metal Oxo Species:

Water Splitting

Water splitting is most easily described as the microscopic reverse reaction of hydrogen combustion (see Scheme 1).

Scheme 1:

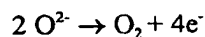


Dioxygen formation occurs in the oxidation half cell reaction, while hydrogen formation occurs in the reduction half cell reaction, Scheme 2. Conceptually, H₂O can be viewed as being comprised of 2H⁺ and O²⁻.

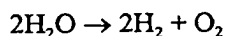
Scheme 2:



Reduction Half Cell Reaction:

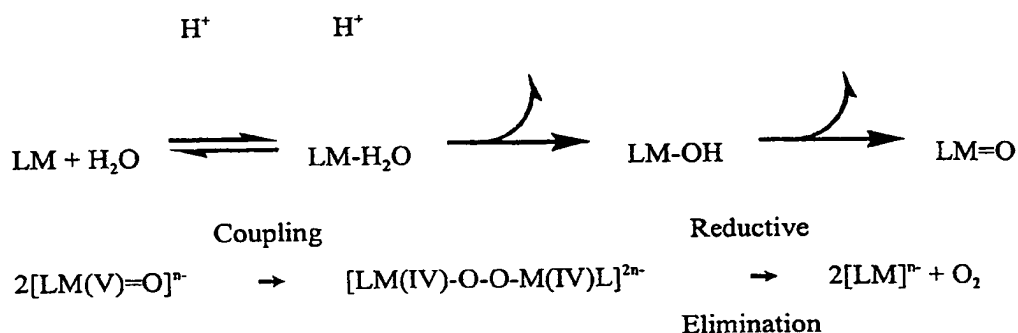


Oxidation Half Cell Reaction:



Net reaction

5 Although it is quite easy to reduce H^+ to form H_2 by procedures well known to those skilled in the art, it is difficult to oxidize water to form oxygen. This is largely due to the fact that the H^+ ions are strongly bound to the O^{2-} ions rendering water oxidation very difficult to perform under neutral or acidic conditions. Under basic conditions the reaction becomes easier due to the greater facility (lower oxidation potential) by which OH^- is oxidized
10 compared to H_2O .



15

wherein LM is the metallated chelate complex of the present invention.

High valent metal oxo species are well situated thermodynamically to catalyze the most difficult part of the water splitting reaction, the formation of dioxygen. Metal ions readily bind water to form aqua species, for example, the aqua species of the metal ligand
20 systems described in the Accounts article. Metal aqua species are more acidic than free H_2O , losing protons readily to form metal hydroxo and metal oxo species. The preparation of metal oxo species in high oxidation states has been described in the Accounts article. It is believed that high valent metal oxo species can play a pivotal role in water oxidation processes according to the scheme shown above.

25 Solar Cells

The direct application of the catalyst systems described herein to harvest light for solar cells and, particularly the indirect application of using light derived energy to perform an oxidation reaction is of profound interest. Recent results have demonstrated that metal aqua complexes of the ligand systems described herein can be oxidized via pure electron transfer reactions to yield high valent metal oxo species. This is significant because one of the big problems in solar cell technology is that of energy storage. Normally, a photovoltaic cell is used to convert solar energy to electrical energy, and then a battery is often used to store the energy in the form of chemical energy. The chemical energy in the battery is then reconverted to electrical energy for power line transmission, and then in many cases the electrical energy is converted back to chemical energy in order to perform useful chemical transformations.

The voltage generated in the first step of solar energy harvesting, the photovoltaic voltage, can be directly applied to the generation of chemical energy. The catalyst systems of the present invention offer a valuable opportunity to harvest electrical energy for the performance of chemical transformations, most notably water splitting. In this scenario, when the sun shines, photovoltaic energy is utilized by the catalyst systems as the driving force for performing the energy intensive part of water splitting, oxygen generation. The hydrogen generation part is not energy intensive and will proceed effectively from H^+ using known technology such as the normal hydrogen electrode. Once the chemical transformation is complete, it is believed that the energy from the sun will have been stored in the form of the technologically significant fuel, hydrogen, and the commercially important oxidant, oxygen, thereby eliminating the unnecessary storage of the electrical energy in a battery.

Another important application for the oxidation catalyst system of the present invention is the manufacture of hydrogen. Hydrogen is now manufactured by way of the water gas shift reaction being performed on hydrocarbons such as coal or natural gas. The byproducts of the water gas shift reaction are CO and CO_2 , green house gases. Hydrogen generated from water can change the balance of the CO_2 released into the atmosphere, thereby significantly reducing the effect of green house gases and global warming.

Fuel Cells

Normal hydrogen/oxygen fuel cells extract the chemical energy stored in the hydrogen/oxygen combustion reaction (see Scheme 1 under water splitting, above) and

convert it at high efficiency into electricity. The catalyst systems of the present invention are effective utilizers of hydrogen peroxide for oxidation reactions, therefore can be useful in the production of a new type of fuel cell, the hydrogen peroxide/substrate fuel cell. Instead of burning a fuel, hydrogen, in the oxidant, oxygen, and extracting the chemical energy as electricity, this new breed of fuel cell will "burn" the substrate fuel in the oxidant hydrogen peroxide and extract the chemical energy as electricity. This is of commercial significance because of the growing need to supply energy to an energy starved world, without generating toxic waste products during the process of energy production. Normal combustion processes are suitable for the generation of heat which can be utilized for power generation. However two significant drawbacks of combustion processes are the inefficiency by which heat can be utilized to generate electricity, on the order of 40-45% Carnot efficiency at best, and the generation of volatile toxic byproducts such as NOX, SOX and AOX which result from the presence of nitrogen, sulfur and halides particularly chlorine in the fuel. A hydrogen peroxide fuel cell solves several of these problems definitively, avoiding NOX production entirely, and allowing for the trapping of SOX and AOX byproducts under controlled low temperature conditions that are absent in normal combustion processes. The hydrogen peroxide fuel cell is also likely to be able to harness energy efficiently at well above the 40-45% typical of combustion processes since the chemical energy is converted directly into electrical energy without the inefficient intermediacy of steam based turbine power generation.

The greatest drawback of a hydrogen peroxide fuel cell is the high cost of hydrogen peroxide relative to air. However, in some niche applications it may be possible to use other energy sources, such as solar energy, to generate the hydrogen peroxide. See the water splitting, and solar energy sections.

25 Liquid CO₂ oxidations

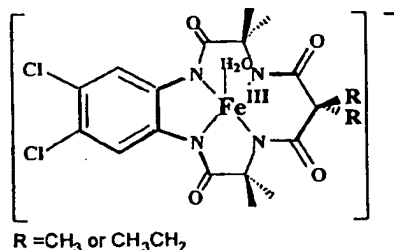
As greater emphasis is placed on environmentally sound manufacturing processes, the use of environmentally non toxic solvent systems such as supercritical (SC) CO₂ has become an economically important facet of the chemical industry. Recent advances in SC CO₂ technology have focused on the solubilization of metal containing catalyst species by the addition of perfluorinated solubilizing groups. In the absence of such perfluorinated tails, most metal catalyst systems are completely insoluble in SC CO₂. The metal catalyst systems

of the invention perform a large variety of useful oxidations and are sythetically versatile enough to easily support the introduction of perfluorinated tails. These perfluorinated catalyst systems will provide an easy entrée into the use of SC CO₂ as an oxidatively robust and environmentally sound solvent system for performing commercially significant oxidations.

Wastewater Clean-up

A recent EPA report outlining environmental issues in the textile industry, EPA/310-R-97-009, describes the wastewater streams from textile mills as being comprised of a complex mixture of different species including sizing, salts, colorants (dyes and dye chromophores), chemicals with high biological oxygen demand (BOD), acids, alkalis, and a variety of organic compounds. While dyes do not comprise a large percentage of the total wastestream, the colors that they impose if allowed to enter streams and lakes may be unacceptable, Zollinger, H., *Color Chemistry*, VCH Publishers, Germany, 1987. It is estimated that 10 – 15% of the 700,000 tons of dyes produced annually worldwide are released in wastestreams, Snowden-Swan, L. J., *Industrial Pollution Prevention Handbook*, Freeman, H. M., Ed., McGraw-Hill, New York, 1995. Among the different technologies applied to decolorizing wastestreams are adsorption of the dye onto a substrate such as charcoal followed by filtration (this is an expensive process) and oxidative degradation. Oxidative degradation processes have relied principally on chlorine and ozone as the oxidants. It is known that oxidation of organic compounds by chlorine can lead to polychlorinated aromatics which are environmental hazards. The cost of ozone is extremely high making it impractical in the long-term. The most environmentally desirable oxidant is hydrogen peroxide, H₂O₂, as its decomposition products are oxygen and water. It has also been noted that desizing starch with H₂O₂ rather than enzymes would be economically viable.

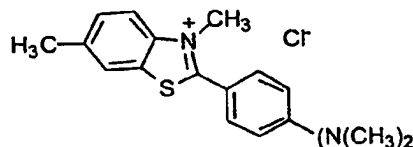
In Horwitz, et al, *J. Am. Chem. Soc.* 1998, 120, 4867-4868 and Collins, et al., U.S. Patent application Serial No. 08/684,670 filed July 22, 1996 and incorporated herein by reference, it has been reported that the iron compounds shown below are excellent and efficient activators of H₂O₂ for the oxidative bleaching of a variety of dyes.



Iron complexes used as oxidant activators for dye bleaching by H₂O₂. [Fe(H₂O)DCB*]⁻ when R = CH₃.

The dyes reported in Horwitz, et al, *J. Am. Chem. Soc. Supra*, and Collins, et al., U.S. Patent application Serial No. 08/684,670 were primarily red and blue dyes. However, in the textile industry the most difficult dyes to remove are the yellow ones. Here we show that the compound with R = CH₃, which is referred to as [Fe(H₂O)DCB*]⁻ in the structure above, is an effective H₂O₂ activator so that some yellow dyes are oxidized.

[Fe(H₂O)DCB*]⁻ bleaches the yellow dye Basic Yellow 1 (Thioflavin T), shown below.



Thioflavin T (Basic Yellow 1).

Shown in Figure 7 are the changes in the ultraviolet/visible (UV/vis) spectrum that occur when the dye is oxidized in pH 10 carbonate/bicarbonate buffer by 0.22 μM [Fe(H₂O)DCB*]⁻ in the presence of 4 mM H₂O₂. In this experiment, [Fe(H₂O)DCB*]⁻ and the dye are combined in the buffer, H₂O₂ is added, and then the spectral changes monitored. Thioflavin T is unaffected by H₂O₂ alone. The solution after 60 min is colorless.

Shown in Figure 8 are the changes in the UV/vis spectrum that occur upon the oxidative bleaching of Acid Yellow 54 (Palatine Fast Yellow BLN) by H₂O₂ and [Fe(H₂O)DCB*]⁻; reaction conditions: pH 10, T = 35 °C, 67 ppm of the adjunct, Dequest as sequesterant, and 4 mM H₂O₂. Acid Yellow 54 is a different class of dye than Basic Yellow 1. The upper trace of Figure 4 shows that when Acid Yellow 54 (l_{max} = 440 nm) and H₂O₂ are combined in the absence of [Fe(H₂O)DCB*]⁻ a new species is produced which,

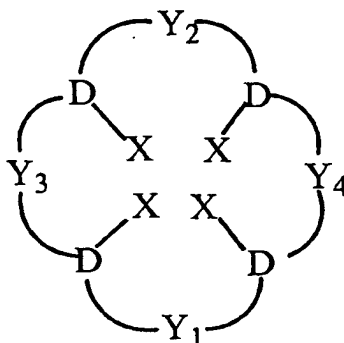
coincidentally, is yellow ($\lambda_{\text{max}} = 380 \text{ nm}$) but has a slightly more intense color than the starting dye. This new species is unaffected by H_2O_2 . When $[\text{Fe}(\text{H}_2\text{O})\text{DCB}^*]^-$ was then added to this solution, an $0.087 \text{ }\mu\text{M}$ aliquot of $[\text{Fe}(\text{H}_2\text{O})\text{DCB}^*]^-$ was added 23 min after the H_2O_2 was added, bleaching of the new species began (lower trace). The initial $[\text{Fe}(\text{H}_2\text{O})\text{DCB}^*]^-$ addition was followed by four $0.22 \text{ }\mu\text{M}$ additions of $[\text{Fe}(\text{H}_2\text{O})\text{DCB}^*]^-$ as indicated on Figure 8 (lower trace). The yellow color from the new species was bleached such that the final solution was very pale yellow. The bleaching reaction was complete after approximately 80 min.

The compounds of the present invention are useful in a variety of oxidation reactions, particularly where a robust catalytic system is needed. Further examples include the disinfection of food surfaces and water for drinking, swimming pools and spas, surface cleaning, e.g., metals, stone, glass, electronics, plastic and polymeric surfaces, surface preparation for painting to enhance adhesion and bleaching, e.g., hair, textiles and pulp and paper bleaching and delignification applications. The effluent from pulp mills can be oxidized for decolorization as well, as described in co-pending U.S patent application of Collins, T. And, C., Serial No. 09/075,598 filed on May 11, 1998 and incorporated herein by reference. Other oxidation reactions that can be activated by the compounds of the present invention include oxidative detoxification, e.g., nerve gas, and homogenous chemical oxidations in general.

Of particular interest is the use of the compounds to activate peroxide or other oxidants for sterilization, for wound cleaning, as fungicides, as bactericides, as insecticides and as herbicides, in sewage treatment, in water treatment, and remediation. The compounds can also be used in oxidant interconversions.

CLAIMS:

1. A compound comprising:
a macrocyclic tetradentate ligand of the structure

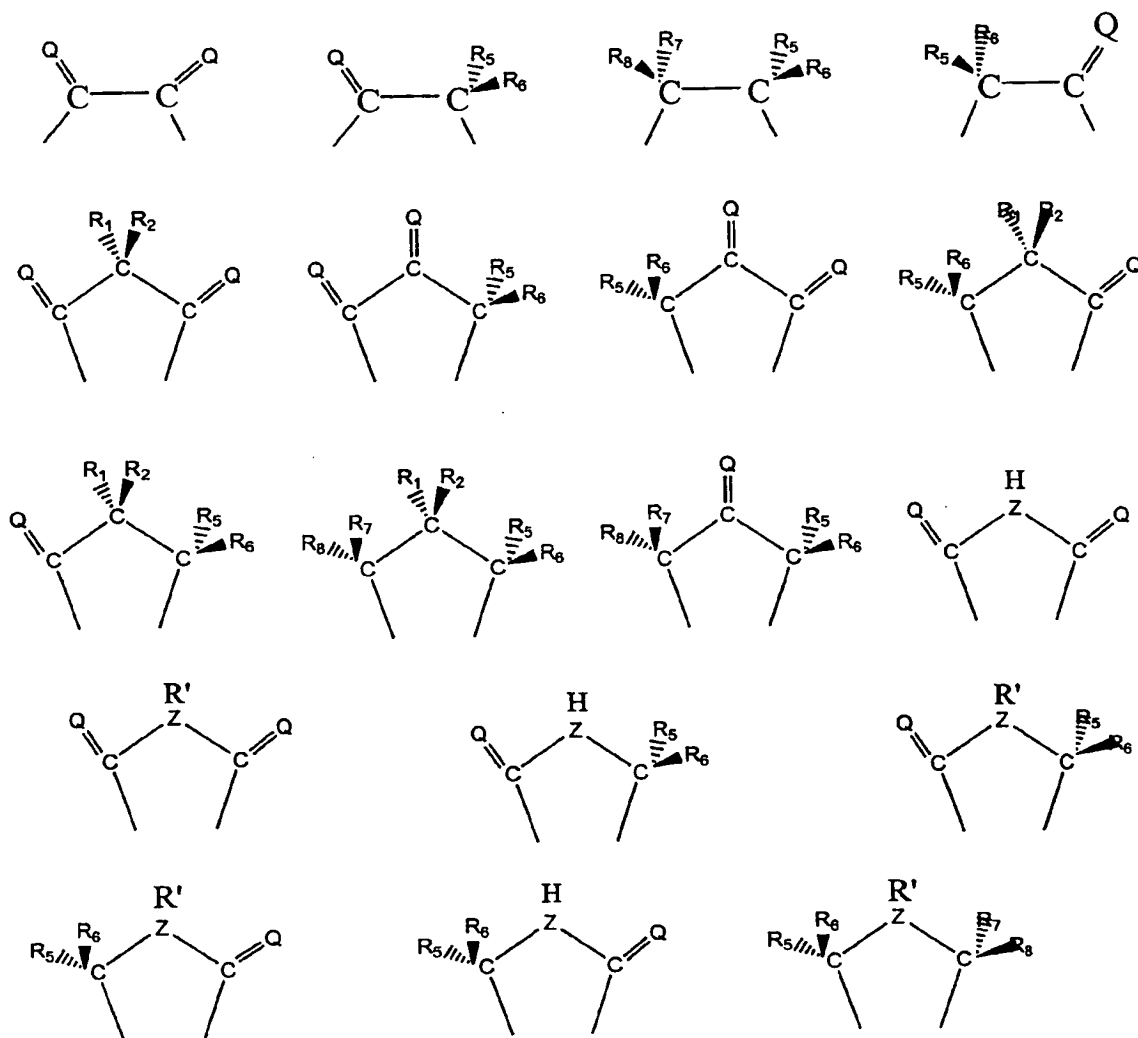


5 wherein:

D is a donor atom selected from the group consisting of N and O;

each X is a position for addition of a substituent and, when D is N, each position is (i) not occupied such that a double bond is formed between D and an atom adjacent to D, or (ii) is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, phenoxy, halogen, halogenated alkyl, halogenated aryl, halogenated alkenyl, halogenated alkynyl, perhaloalkyl, perhaloaryl, a substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted cycloalkenyl ring, a substituted or unsubstituted saturated heterocyclic ring, a substituted or unsubstituted unsaturated heterocyclic ring, and at least one X is hydrogen, and when D is O, the position is not occupied;

15 Y₁, Y₂, Y₃ and Y₄ are the same or different and each is a unit selected from the group consisting of



wherein:

Q is oxygen or ZR'

Z is selected from the group consisting of N, P and As; and,

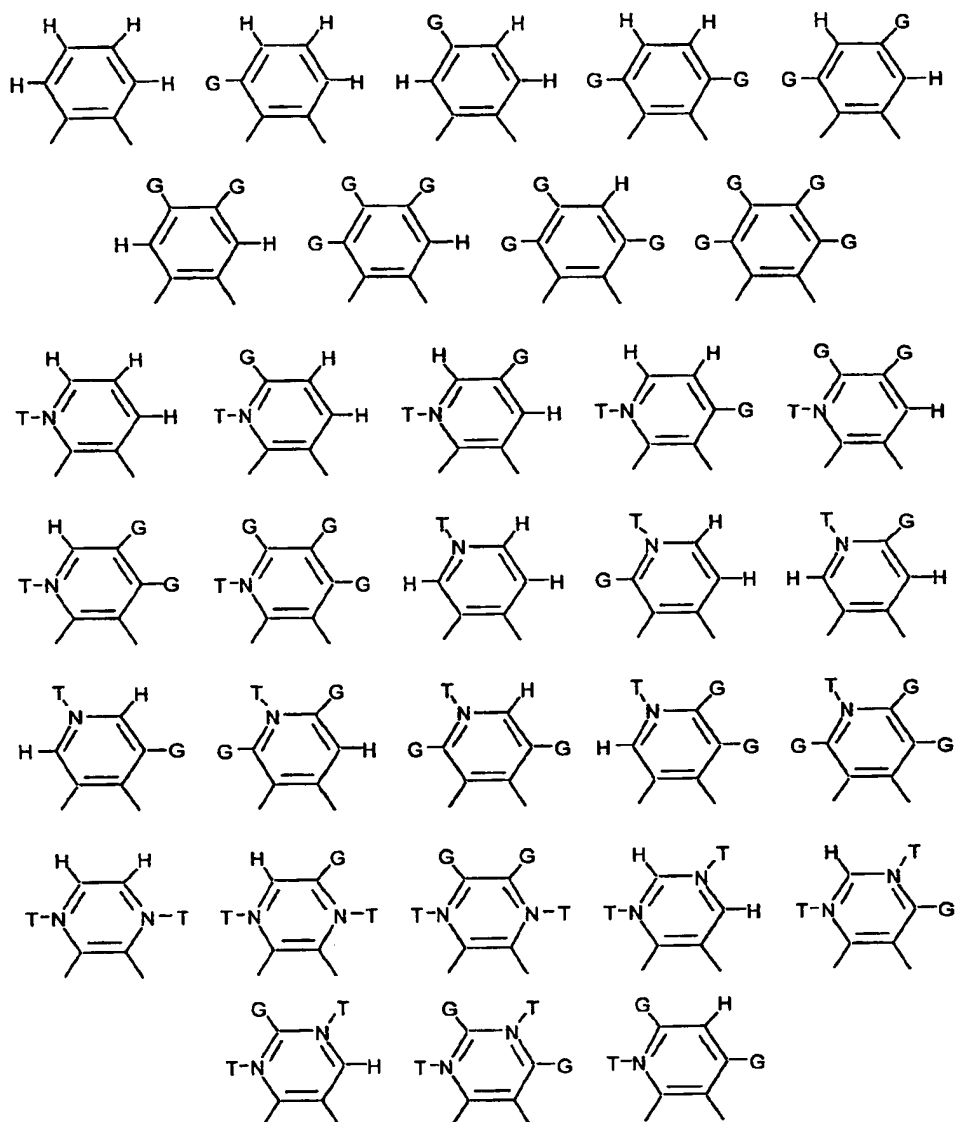
- 5 R' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, phenoxy, halogen, halogenated alkyl, halogenated aryl, halogenated alkenyl, halogenated alkynyl, perhaloalkyl, perhaloaryl, a substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted cycloalkenyl ring, a substituted or unsubstituted saturated heterocyclic ring, a substituted or unsubstituted unsaturated heterocyclic ring;

- 10 R₅, R₆, R₇ and R₈, pairwise and cumulatively, are the same or different and each (i) is selected from the group consisting of alkyl, aryl, halogen, halogenated alkyls, perhaloalkyl,

halogenated aryls, perhaloaryl, CF_3 , CH_2CF_3 , cycloalkyl, cycloalkenyl, alkynyl, alkylaryl, alkoxy, phenoxy, oxylic, phenyl, or (ii) together with an R substituent on an adjacent carbon in the same Y unit, form a mono-, di-, tri- or tetra- substituted or unsubstituted benzene ring of which two carbons in the ring are adjacent carbons in the same Y unit, or (iii) together with
5 a paired R bound to the same carbon atom form a substituted or unsubstituted cycloalkyl or substituted or unsubstituted cycloalkenyl ring;

R_1 and R_2 are the same or different, linked or nonlinked, and each is selected from the group consisting of substituents which are unreactive, form strong bonds intramolecularly with said R_1 and R_2 and with the carbon of the Y unit to which each is bound, are sterically
10 hindered and are conformationally hindered such that oxidative degradation of a metal complex of the compound is restricted when the complex is in the presence of an oxidizing agent, or together with an R substituent on an adjacent carbon in the same Y unit, form a mono-, di-, tri- or tetra- substituted or unsubstituted benzene ring of which two carbons in the ring are adjacent carbons in the same Y unit.

15 2. The compound recited in claim 1 wherein the benzene ring formed by R substituents on adjacent carbons is selected from the group consisting of

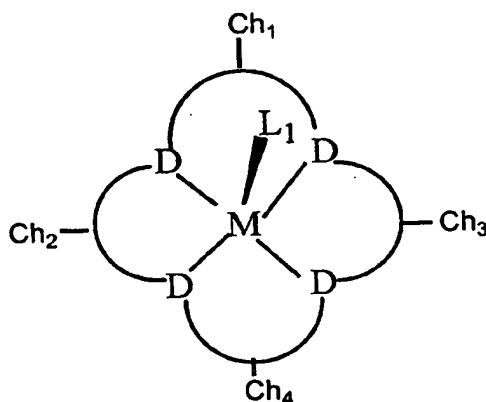


wherein:

each T is the same or different and is an unoccupied position, hydrogen, alkyl or haloalkyl, and,

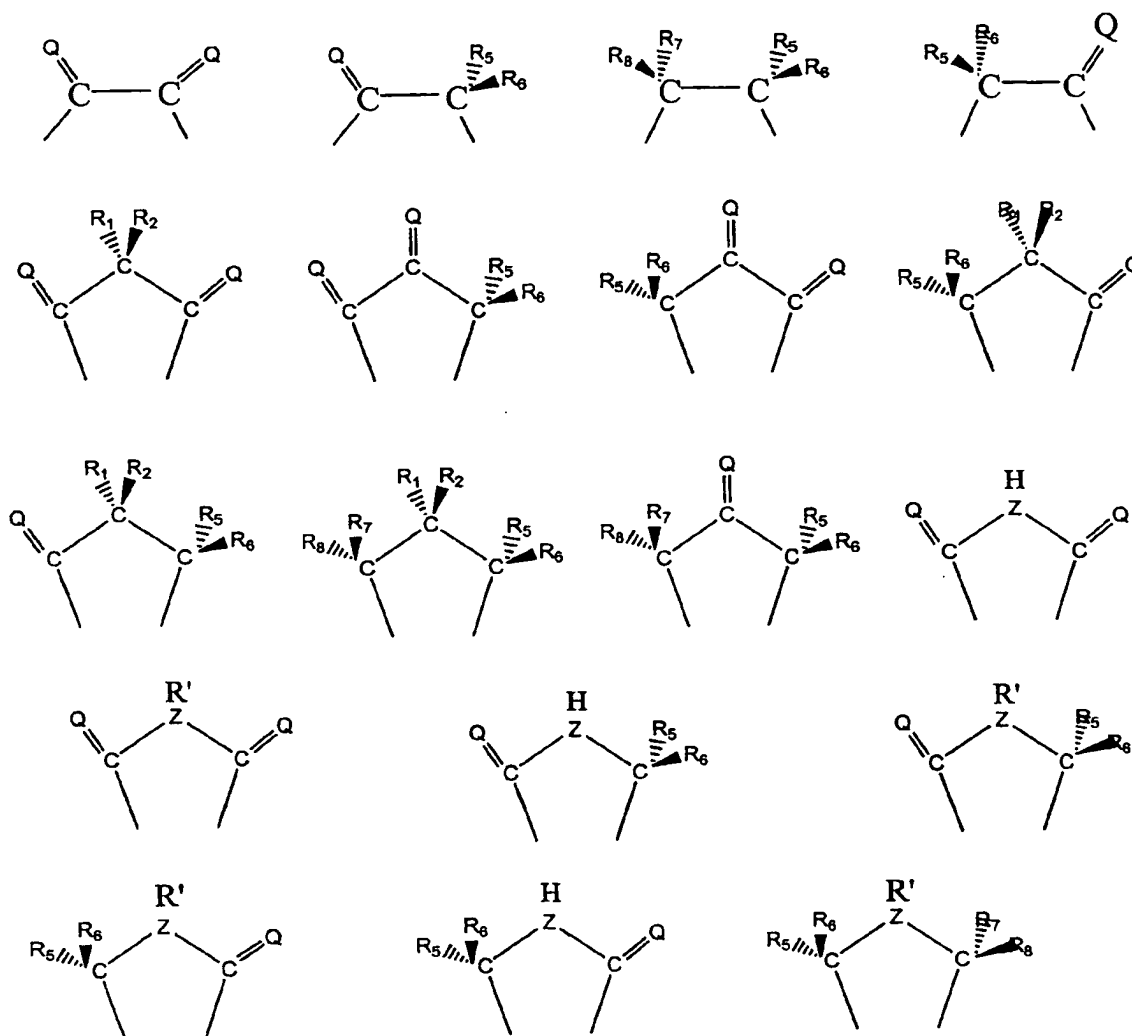
- 5 each G is the same or different and comprises halogen, hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, alkylaryl, phenoxy substituents, amino, substituted amino, nitro, alkoxy, aryloxy and combinations thereof, or combine to form a cycloalkyl or cycloalkenyl ring, which may contain at least one atom that is not carbon.

3. The compound recited in claim 1 wherein each of R_1 and R_2 is selected from the group consisting of hydrogen, alkyl, aryl, halogen, haloalkyl, perhaloalkyl, haloaryl, perhaloaryl methyl, CF_3 , and, if linked, cyclobutyl, cyclopropyl, cyclopentyl, cyclohexyl, substituted cyclopropyl, substituted cyclobutyl, substituted cyclopentyl and substituted cyclohexyl.
4. A chelate complex of the formula:



wherein:

- D is a donor atom selected from the group consisting of N , O and NR_D , and R_D is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkoxy, phenoxy, halogen, halogenated alkyl, halogenated aryl, halogenated alkenyl, halogenated alkynyl, perhaloalkyl, perhaloaryl, a substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted cycloalkenyl ring, a substituted or unsubstituted saturated heterocyclic ring, a substituted or unsubstituted unsaturated heterocyclic ring;
- M is a transition metal;
- L_1 is optional and is a labile ligand;
- Ch_1 , Ch_2 , Ch_3 and Ch_4 are oxidation resistant chelate groups which are the same or different and which form 5- or 6-membered rings with said metal; and, each is selected from the group consisting of



wherein:

Q is oxygen or ZR'

Z is selected from the group consisting of N, P and As; and,

- 5 R' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, phenoxy, halogen, halogenated alkyl, halogenated aryl, halogenated alkenyl, halogenated alkynyl, perhaloalkyl, perhaloaryl, a substituted or unsubstituted cycloalkyl ring, a substituted or unsubstituted cycloalkenyl ring, a substituted or unsubstituted saturated heterocyclic ring, a substituted or unsubstituted unsaturated heterocyclic ring;

- 10 R₅, R₆, R₇ and R₈ pairwise and cumulatively, are the same or different and each (i) is selected from the group consisting of alkyl, aryl, halogen, halogenated alkyls, perhaloalkyl,

halogenated aryls, perhaloaryl, CF_3 , CH_2CF_3 , cycloalkyl, cycloalkenyl, alkynyl, alkylaryl, alkoxy, phenoxy, oxylic, phenyl, or (ii) together with an R substituent on an adjacent carbon in the same Ch unit, form a mono-, di-, tri- or tetra- substituted or unsubstituted benzene ring of which two carbons in the ring are adjacent carbons in the same Y unit, or (iii) together with
5 a paired R bound to the same carbon atom form a substituted or unsubstituted cycloalkyl or substituted or unsubstituted cycloalkenyl ring;

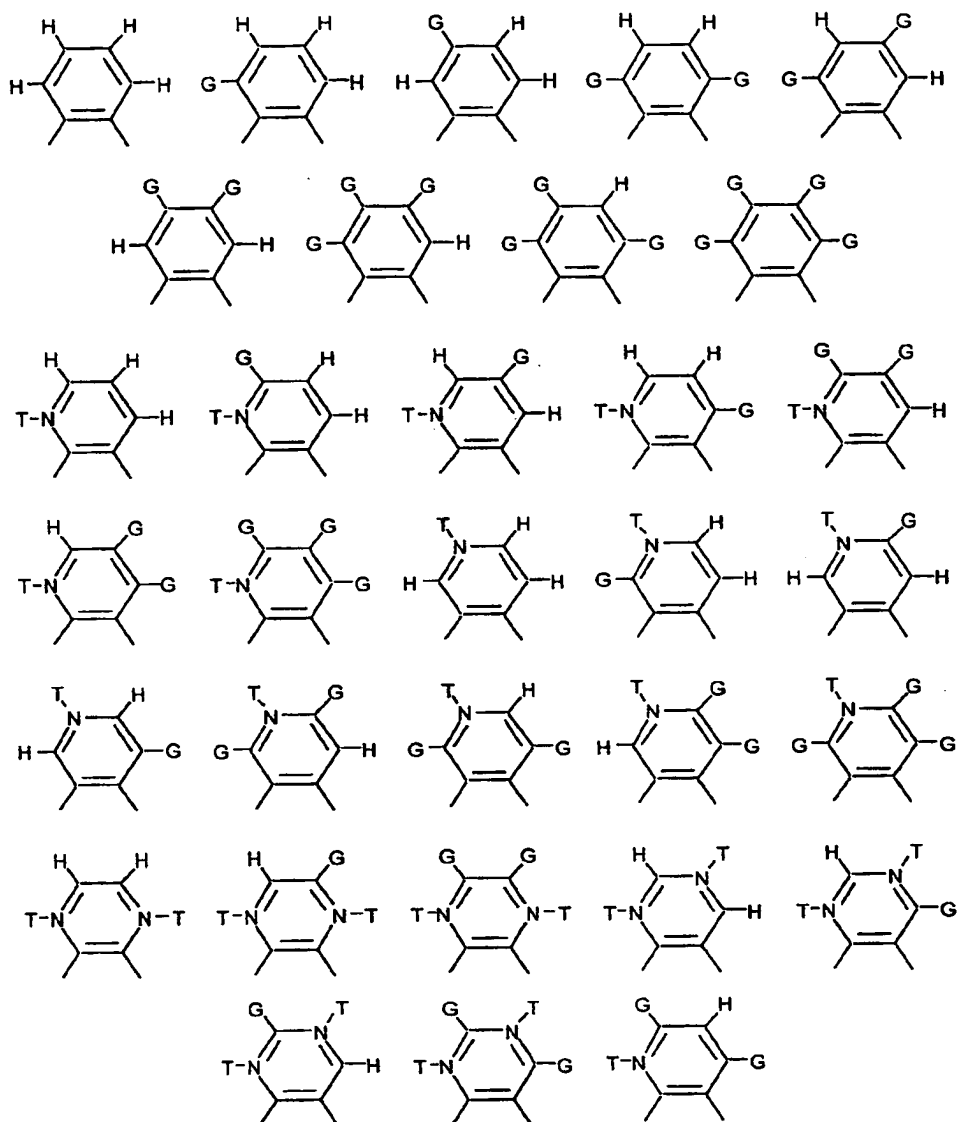
R_1 and R_2 are the same or different, linked or nonlinked, and each is selected from the group consisting of substituents which are unreactive, form strong bonds intramolecularly with said R_1 and R_2 and with the carbon of the Y unit to which each is bound, are sterically
10 hindered and are conformationally hindered such that oxidative degradation of a metal complex of the compound is restricted when the complex is in the presence of an oxidizing agent, or together with an R substituent on an adjacent carbon in the same Ch unit, form a mono-, di-, tri- or tetra- substituted or unsubstituted benzene ring of which two carbons in the ring are adjacent carbons in the same Ch unit.

15 5. The complex recited in claim 4 wherein R_1 and R_2 are selected from the group consisting of hydrogen, halogen, methyl, perhaloalkyl, CF_3 and, if linked, cyclobutyl, cyclopropyl, cyclopentyl, cyclohexyl, substituted cyclopropyl, substituted cyclobutyl, substituted cyclopentyl and substituted cyclohexyl.

20 6. The complex recited in claim 4 wherein the metal is selected from the group consisting of Cr, Mo, W, Mn, Tc, Re, Fe, Ru, Os, Co, Rh, Ir, Ni, Pd, Pt, Cu, Ag and Au.

7. The complex in claim 4 wherein L_1 is an oxygen containing substituent selected from the group consisting of peroxide, OH_2 , O, and OH.

25 8. The complex recited in claim 4 wherein the R substituents on adjacent carbons of Ch_1 form a constituent selected from the group consisting of



wherein:

each T is the same or different and is an unoccupied position, hydrogen, alkyl or haloalkyl, and,

- 5 each G is the same or different and comprises halogen, hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, alkylaryl, phenoxy substituents, amino, substituted amino, nitro, alkoxy, aryloxy and combinations thereof, or combine to form a cycloalkyl or cycloalkenyl ring, which may contain at least one atom that is not carbon.

9. The complex recited in claim 4 wherein the metal is a transition metal.

10. The complex recited in claim 9 wherein the metal is selected from groups 6, 7, 8, 9, 10, and 11 transition metals.

11. The complex recited in claim 10 wherein the metal is Fe or Mn.

12. The complex recited in claim 4 wherein R_1 and R_2 form, together with the carbon atom to which both are bound, a three-, four-, five-, or six-membered substituted or unsubstituted ring.

13. A process for metallating the compound of claims 1 - 3 comprising adding to said compound metal ion under basic conditions to produce the complex of claim 4.

14. The use of the complex recited in claims 4 - 12 in the presence of an oxidant for performing of an oxidation reaction.

15. The use of the complex recited in claim 14 wherein the complex is present in substoichiometric amounts.

16. A process comprising exposing a target to an oxidant in the presence of the complex recited in claim 4.

17. The process recited in claim 16 wherein the oxidant is selected from the group consisting of halogen, halogen oxide, halogenoxoanion, elemental halogen, a peroxy compound, oxygen, air, oxygen in the presence of an adjunct and combinations thereof.

18. The process recited in claim 17 wherein the peroxy compound is hydrogen peroxide.

19. The process recited in claim 16 wherein the oxidant is selected from the group consisting of elemental chlorine, chlorine oxide, chlorine oxoanion, chlorine dioxide, hypochlorite, acidic species thereof and combinations thereof.

20. The process recited in claim 16 wherein the complex is added for activation of the oxidant for sterilization, wound cleaning, fungicidal, bactericidal, insecticidal and herbicidal oxidations, or for water treatment.

21. The process recited in claim 16 wherein the target is an organic material.

22. The process recited in claim 21 wherein the organic material is comprised of wood pulp, textiles, colorants or microbes.

23. The process recited in claim 21 wherein the target is an inorganic material.
24. The process recited in claim 23 wherein the inorganic material is water.
25. The process recited in claim 16 for the oxidative detoxification of
- 5 nerve gas.
26. A process for the generation of O₂ comprising:
exposing a source of O to the complex recited in claim 4, and, applying energy thereto.

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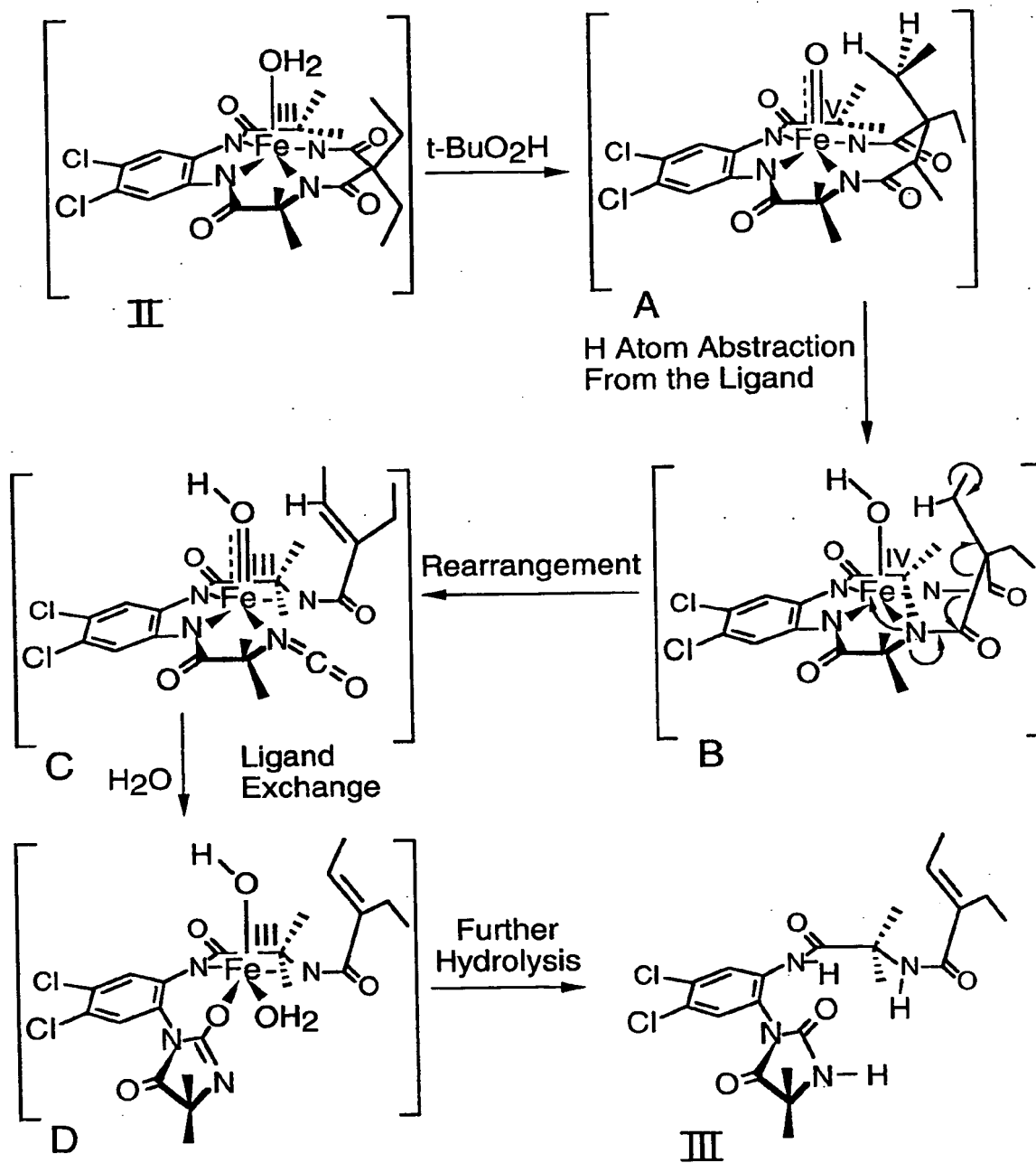


FIG. 1

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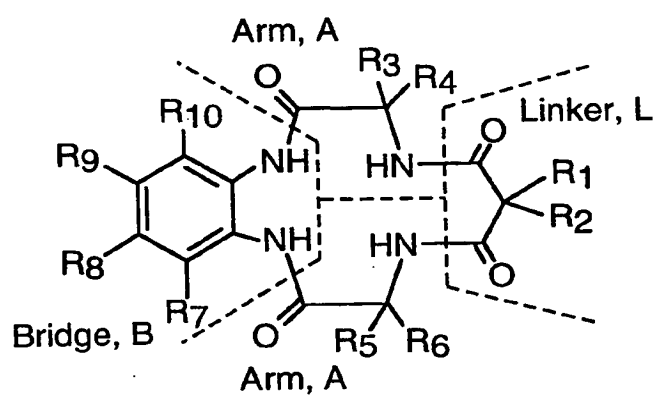
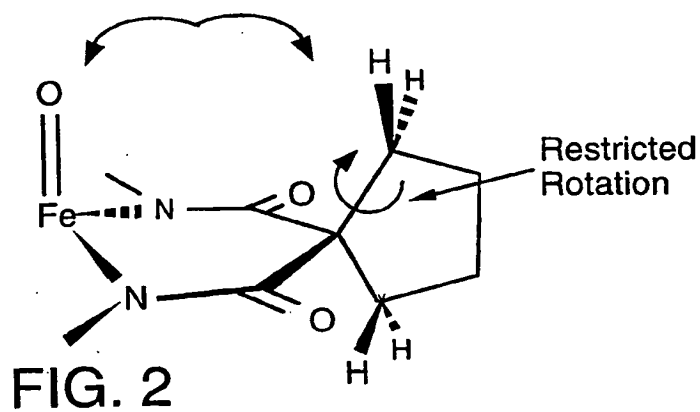


FIG. 3a

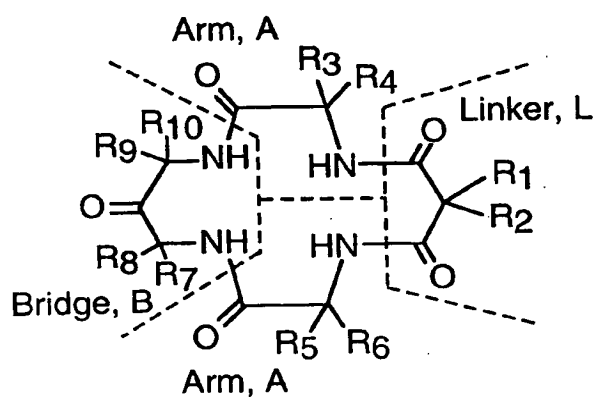


FIG. 3b

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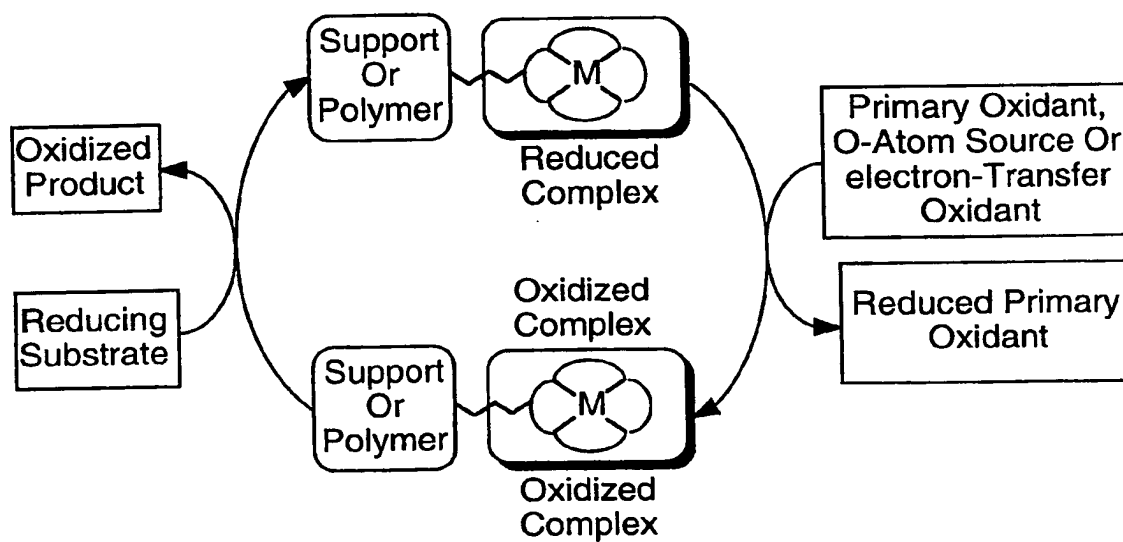


FIG. 4

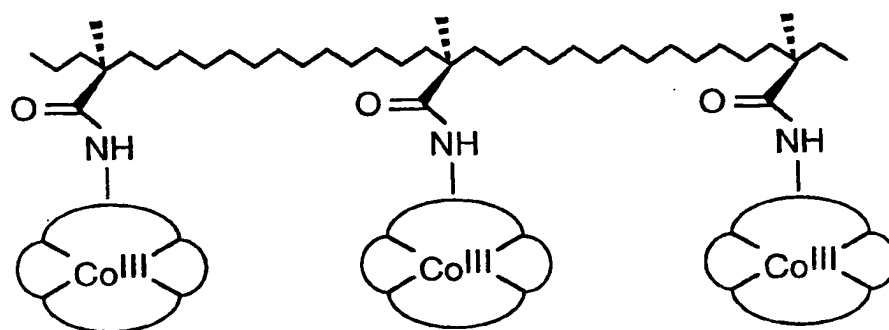


FIG. 5

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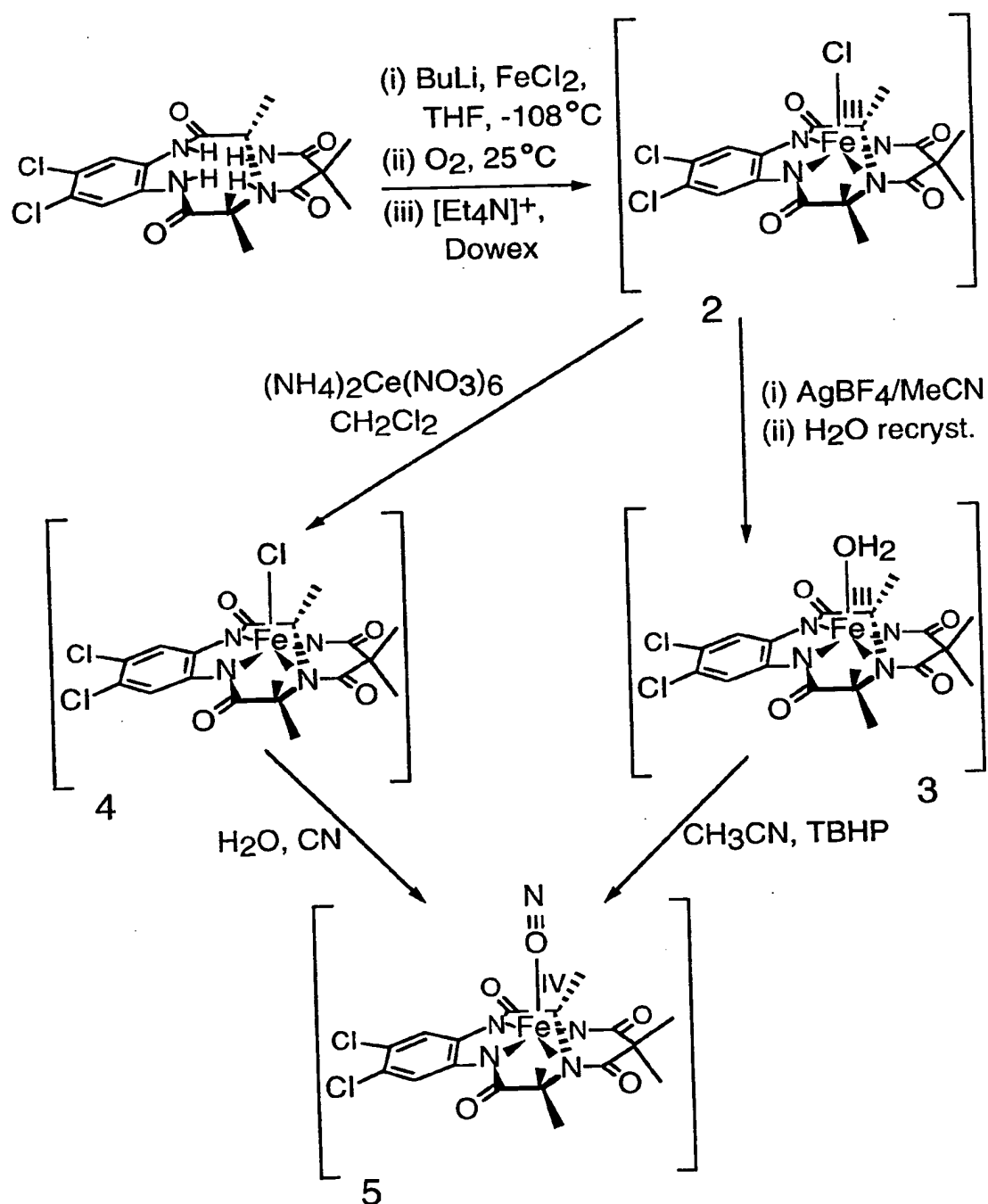


FIG. 6

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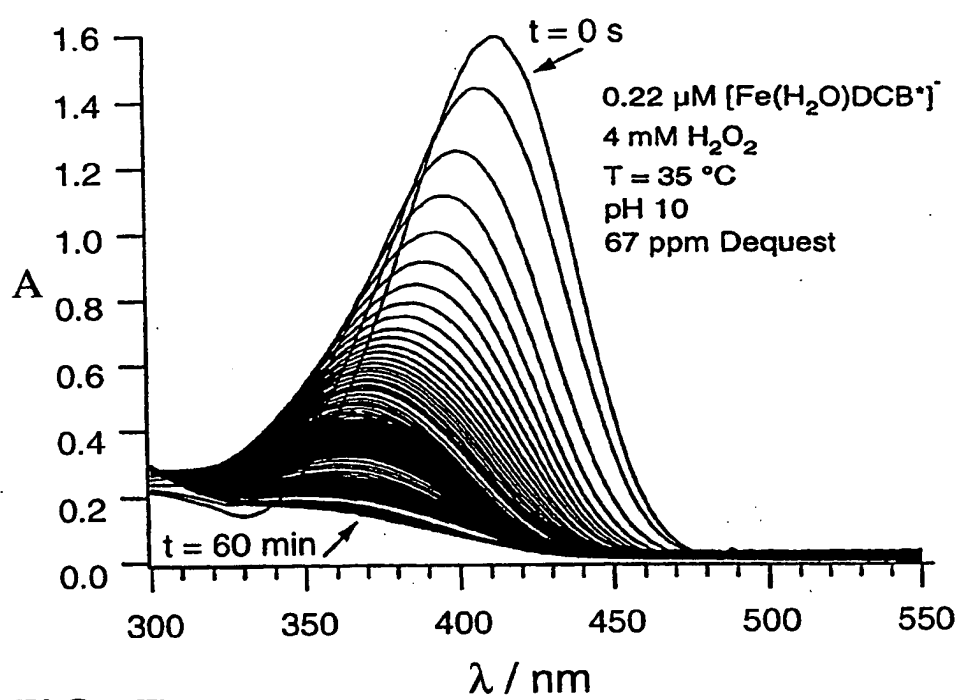
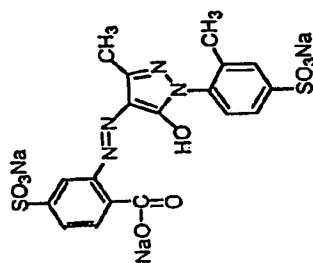
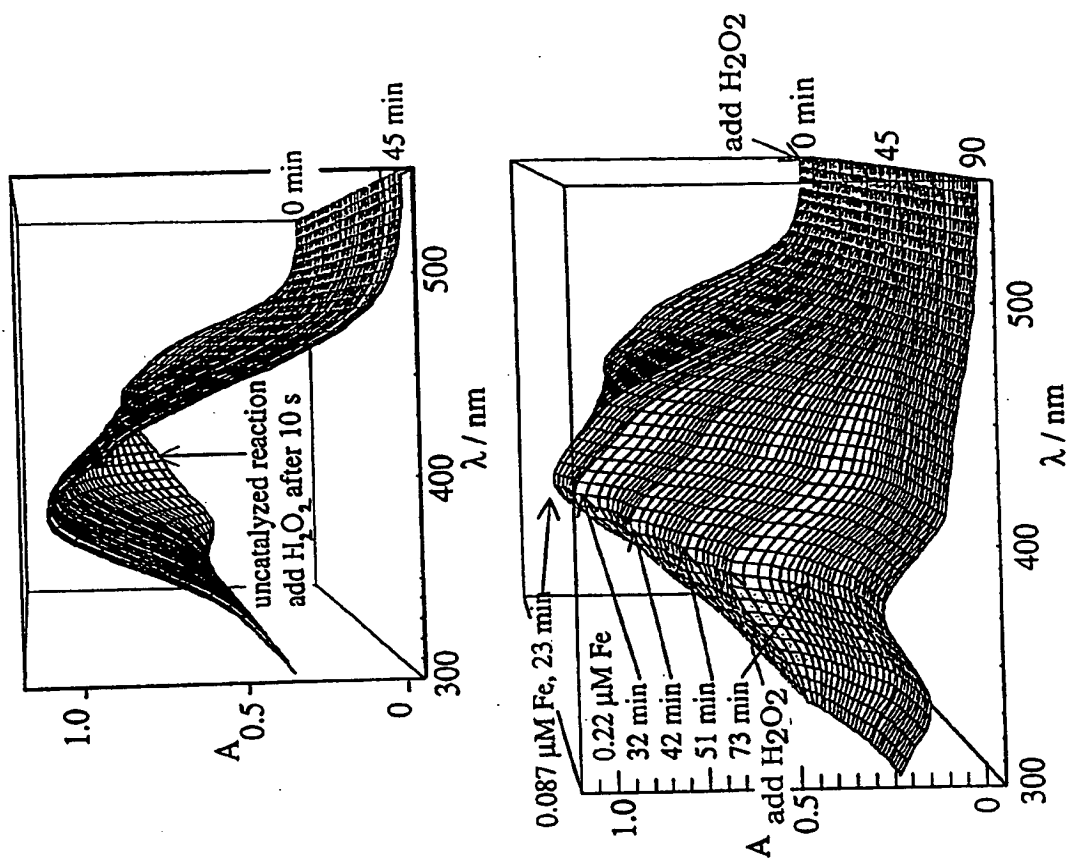
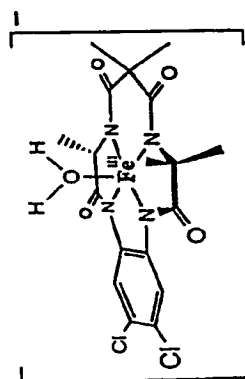


FIG. 7

Acid Yellow 54 Oxidation



Reaction conditions
pH 10
4 mM H_2O_2
67 ppm Dequest
35 °C



INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/12475

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B01J31/18 C07F15/00 C07D257/02 C07D257/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 B01J C07F C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	COLLINS TJ: "Designing Ligands for Oxidising Complexes" ACCOUNTS OF CHEMICAL RESEARCH, vol. 27, 1994, pages 279--285, XP002048603 cited in the application the whole document	1-26
A	US 4 758 682 A (COLLINS TERRENCE J ET AL) 19 July 1988 (1988-07-19) the whole document	1-26
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Date of the actual completion of the international search

2 September 1999

Date of mailing of the international search report

23/09/1999

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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